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## TOXICITY STUDIES ON ANTIRADIATION AGENTS

## 30 6

Final Report

Frederick E. Reno

March 1979

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Supported by:

US Army Medical Research and Development Command Fort Detrick, Frederick, MD 21701

Contract No. DADA17-69-C-9105

Hazelton Laboratories America, Inc. Vienna, VA 22180

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## FINAL REPORT - Contract No. DADA17-69-C-9105

#### SUMMARY

This contract was awarded to provide for the conduct of toxicological evaluations on various drugs under study by WRAIR. In general these acute and subacute studies were designed to evaluate and characterize the pharmacotoxic signs of these drugs to support the IND.

Eighteen studies were performed over the period of this contract.

These are listed below:

HLA PROJECT NO.	TEST MATERIAL	STUDY CONDUCTED					
193-401	WR 2823	Acute Oral and IV Toxicity in Rats					
193-402	WR 2823	Acute Oral and IP Toxicity in Mice					
193-403	WR 2823	Acute Oral and IP Toxicity in Guinea Pigs					
193-404	WR 2823	14-Day IV Toxicity in Rats					
193-405	WR 2823	Acute IV Toxicity in Dogs					
193-406	WR 2823	14-Day Subacute IV Toxicity in Dogs					
193-407	WR 2721	28-Day Oral Toxicity in Monkeys					
193-408	WR 2529	Acute Oral Toxicity in Mice					
193-409	WR 2823	Acute Oral Toxicity in Mice (repeat)					
193-410	WR 2823	Histopathology on 193-404					
193-411	WR 2823	Histopathology on 193-406					
193-412	WR 2823	2-Week IV Study in Rats					
193-413	WR 149, 024	Acute IV Toxicity in Rats and Mice;					
	•	Acute IP Toxicity in Guinea Pigs					
193-414	WR 149, 024	Acute IV Toxicity in Dogs					
193-415	WR 149, 024	Acute IV Toxicity in Monkeys					
193-416	WR 149, 024	2-Week IV Toxicity in Dogs					
193-417	WR 149, 024	2-Week Toxicity in Monkeys					
193-418	WR 2823	Infusion Study in Dogs					

Detailed technical reports were submitted for studies identified by Project No. 193-401 through 193-417. For Project No. 193-418 Hazelton Laboratories provided laboratory support and animals for an infusion study under the direction by WRAIR personnel. Data was collected by these WRAIR personnel, and no formal report by HLA was required.

## FOREWORD

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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#### HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: October 17, 1969

Material: WR-2823 (AU 69115)

Subject: REPORT NO. 19

Acute Oral Dose Range - Rats Acute Oral Administration - Rats

Acute Intravenous Administration - Rats

Project No. 193-401

Date Received July 2, 1969.

<u>Description</u> Fine, white powder with no noticeable odor.

Purity Assumed to be 100% active ingredient.

#### SUMMARY

WR-2823 (AU 69115) was evaluated for acute oral toxicity by oral intubation to three groups of two male rats each at dosage levels of 100, 1000, and 10,000 mg/kg of body weight (acute oral dose range) in order to more accurately define the toxic range prior to initiating an expanded  $LD_{50}$  study.

WR-2823 (AU 69115) was then further evaluated for acute oral toxicity by oral intubation to eight groups of 10 male rats each at dosage levels of 100 to 2150 mg/kg of body weight. The acute oral LD50 was found to be 2037 mg/kg of body weight (confidence limits, 1281 to 3239 mg/kg of body weight). Signs of toxic effect included depression, labored respiration, hunched appearance, diarrhea or brown stains on body, squinting, ptosis, lacrimation, reddened eyes, yellow stain on fur, urine stains, and slight ataxia.

In addition, the test material was evaluated for acute intravenous toxicity by intravenous injection into the tail vein of six groups of 10 male rats each at dosage levels of 63.1 to 631 mg/kg of body weight. The acute intravenous  $LD_{50}$  was found to be 543 mg/kg of body weight (confidence limits, 402 to 735 mg/kg of body weight). Toxic signs included labored respiration, depression, ptosis, hunched appearance, reddened eyes, and comatose appearance.

#### ACUTE ORAL DOSE RANGE - RATS

Procedure Oral intubation to three groups of two male rats each. Initial weight ranged from 200 to 235 grams, and the animals were fasted overnight prior to dosing. Observations for mortality and signs of effect were made immediately after intubation, frequently on the day of intubation, and daily thereafter for 28 days. Necropsies were performed on all animals which died during the study and on those animals sacrificed at termination (chloroform overdose). The solvent was distilled water.

# Results

Mortality Data:

		Cumulative Mortality						
Dose mg/kg	Concentration %	Immediate	Hours 1 4-24		<u>Days</u> 2 3-2			
100	10	0/2	0/2	0/2	0/2	0/2		
1,000	10	0/2	0/2	1/2	2/2			
10,000	50	0/2	2/2					

Principal Toxic Effects: Toxic signs noted at all levels included depression and labored respiration. In addition to these signs, squinting, excessive urination, diarrhea, hunched appearance, and bloody crust on nose were noted at the 1000 mg/kg level; and lacrimation, salivation, and convulsions were noted at the 10,000 mg/kg level.

Major Necropsy Findings:

At Death -

- (1000 mg/kg Level) Stomach and intestines distended with fluid resembling compound, pyloric portion of stomach blanched, intestinal tract thin and smooth in appearance, liver dark reddish brown in color, and renal medulla dark red in color.
- (10,000 mg/kg Level) Pyloric portion of stomach smooth and blanched with dark pink areas, intestines distended with brown fluid, dark red areas on intestinal walls with blood vessels dilated in appearance, liver mottled, and dark zone at corticomedullary junction.

At Sacrifice - No observable gross pathology.

#### ACUTE ORAL ADMINISTRATION - RATS

<u>Procedure</u> The compound was administered by oral intubation to eight groups of 10 male rats (Charles River, Sprague-Dawley Caesarean-derived) each. The solvent was distilled water. One group of 10 male rats, which received

distilled water at a dosage level of 1000 mg/kg of body weight, served as a control and was subjected to the same experimental conditions as the test groups. Initial body weight ranged from 135 to 242 grams, and the animals were fasted overnight prior to dosing. Observations for mortality and signs of effects were made immediately after dosing; at one, four, and 24 hours; and once daily thereafter for a total of 14 days. Gross necropsy was performed on all animals which died during the study and on those sacrificed (chloroform overdose) at termination. Mortality data was analyzed statistically by the method of Finney, D. J., Probit Analysis, Cambridge University Press, 1952.

#### Results

Mortality Data: Values below represent the number of animals dead per number of animals tested, cumulative.

	Concentration		Time o	f Death		
Dose mg/kg	of Solution %	Immediate	7	Hours 4	24	Days 2-14
100	10	0/10	0/10	0/10	0/10	0/10
159	10	0/10	0/10	0/10	0/10	0/10
251	10	0/10	0/10	0/10	0/10	0/10
398	10	0/10	0/10	0/10	0/10	0/10
631	10	0/10	0/10	0/10	0/10	0/10
1000	10	0/10	0/10	0/10	2/10	2/10
1590	30	0/10	1/10	1/10	4/10	4/10
2150	10	0/10	5/10	10/10		

 $LD_{50}$ , mg/kg - 2037

Confidence Limits (95%), mg/kg - 1281 to 3239

Slope - 2.885

Graphical presentation of the dose-response analysis is appended to this report.

## Principal Toxic Effects:

Control - No toxic effects were noted.

100 and 159 mg/kg Levels - No toxic effects were noted.

251, 398, and 631 mg/kg Levels - The following toxic signs were noted one or four hours postintubation: depression, labored respiration (398 and 631 mg/kg levels), hunched appearance, diarrhea or brown stains on body (398 and 631 mg/kg levels), squinting (398 mg/kg level), ptosis (631 mg/kg level), and lacrimation (631 mg/kg level). In addition, eyes of animals at the 631 mg/kg

level appeared red from 48 hours through Day 3. Animals at the 251 and 398 mg/kg levels appeared normal by Day 5 or Day 13, but animals at the 631 mg/kg level exhibited signs through termination of the study.

1000, 1590, and 2150 mg/kg Levels - Toxic signs noted immediately after intubation of the compound included depression, labored respiration, squinting (1000 mg/kg level), and hunched appearance (2150 mg/kg level). Delayed toxic signs included ptosis, diarrhea or brown stains on body, eyes red in appearance (1000 mg/kg level), yellow stain on fur (1000 mg/kg level), alopecia (one animal at the 1000 mg/kg level), lacrimation (1590 mg/kg level), urine stains (1590 mg/kg level), and slight ataxia (2150 mg/kg level).

## Major Necropsy Findings:

At Death - Stomach and intestines distended with gas and amber-colored liquid (1000 mg/kg level); stomach and intestinal walls thin (1000, 1590, and 2150 mg/kg levels); clear, yellowish colored fluid in stomach and intestines (1590 mg/kg level); lining of pyloric portion of stomach blanched (2150 mg/kg level); Peyer's patches enlarged (2150 mg/kg level); kidneys dark red in color (1000 mg/kg level); renal medulla dark red in color (2150 mg/kg level); liver dark red or reddish brown in color (1000 and 2150 mg/kg levels); liver mottled (1590 mg/kg level); and cut surface of kidneys striated (398 and 1590 mg/kg levels).

At Sacrifice - Spleen appeared enlarged (100, 398, and 1000 mg/kg levels), renal cortex pale green-brown or pale brown in color (100, 159, 251, and 1000 mg/kg levels), renal pelvis dilated (100 and 1590 mg/kg levels), renal pelvis dilated with fissures extending into cortex (159 mg/kg level), pyloric region of stomach red in color (100 and 631 mg/kg levels), kidneys pale brown or green-brown in color (159, 398, and 631 mg/kg levels), liver pale brown in color (159 and 1000 mg/kg levels), stomach walls thickened (1000 and 1590 mg/kg levels), and renal medulla dark red in color (1590 mg/kg level).

## ACUTE INTRAVENOUS ADMINISTRATION - RATS

## **Procedure**

Experimental Animals:

Species - Adult male albino rats of the Charles River (Sprague-Dawley Caesarean-derived).

Body Weight Range - At initiation, 158 to 225 grams.

Diet - Purina Laboratory Chow and water available ad libitum.

Administration: WR-2823 (AU 69115) was administered by intravenous injection into the tail vein to six groups of 10 males each at dosage levels of 63.1, 100, 159, 251, 398, and 631 mg/kg of body weight. One group of 10 rats, which received saline solution at a dosage level of 6.31 mg/kg

of body weight, served as a control and was subjected to the same experimental conditions as the test groups.

## Observations and Records:

Mortality and Toxic Effects - Observations were recorded immediately after dosing; at one, four, and 24 hours; and once daily thereafter for a total of 14 days.

Body Weights - Recorded initially and terminally.

## Terminal Studies:

Sacrifice - By chloroform overdose.

Gross Necropsy - Performed on all animals which died during the study and on those sacrificed at termination.

Statistical Analysis: Mortality data analyzed by the method of Finney, D. J., Probit Analysis, Cambridge University Press, 1952.

## Results

Mortality Data: Values below represent the number of animals dead per number of animals tested, cumulative.

	Concentration	_	Time of Death					
Dose mg/kg	of Solution %	Immediate	1-4	24	Days 2-14			
63.1	2.5	0/10	0/10	0/10	0/10			
100	10	0/10	0/10	0/10	0/10			
159	10	0/10	0/10	0/10	0/10			
251	10	0/10	0/10	0/10	0/10			
398	30	0/10	2/10	3/10	3/10			
631	30	7/10	10/10					

 $LD_{50}$ , mg/kg - 543

Confidence Limits (95%), mg/kg - 402 to 735

Slope - 4.02

Graphical presentation of the dose-response analysis is appended to this report.

## Principal Toxic Effects:

Control - No toxic effects were observed.

63.1, 100, 159, and 251 mg/kg Levels - Labored respiration, depression, and ptosis (159 and 251 mg/kg levels) were noted immediately or one hour after intubation followed by hunched appearance and reddened eyes (159 and 251 mg/kg levels) at 24 hours. Animals at the three lower levels recovered by 48 hours (63.1 mg/kg level), by Day 4 (100 mg/kg level), or by Day 5 (159 mg/kg level); but signs persisted in animals at the 251 mg/kg level through termination of the study.

398 and 631 mg/kg Levels - Depression, labored respiration, ptosis (398 mg/kg level), ataxia (398 mg/kg level), and comatose

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appearance (631 mg/kg level) preceded partial mortality at 24 hours at the 398 mg/kg level and total mortality by one hour at the 631 mg/kg level. Signs persisting in survivors at the 398 mg/kg level through termination of the study included reddened eyes and hunched appearance.

## Major Necropsy Findings:

At Death - Liver mottled, cut surface of kidney striated, and dark red zone between renal cortex and medulla (all observed at the 398 and 631 mg/kg levels).

At Sacrifice - Liver pitted, renal cortex gray or grayish green in color, and renal pelvis dilated (all observed at the 159, 251, and 398 mg/kg levels).

Submitted by

MARCELINA B. POWERS, D.V.M., M.S. Project Manager, Drugs & Industrial

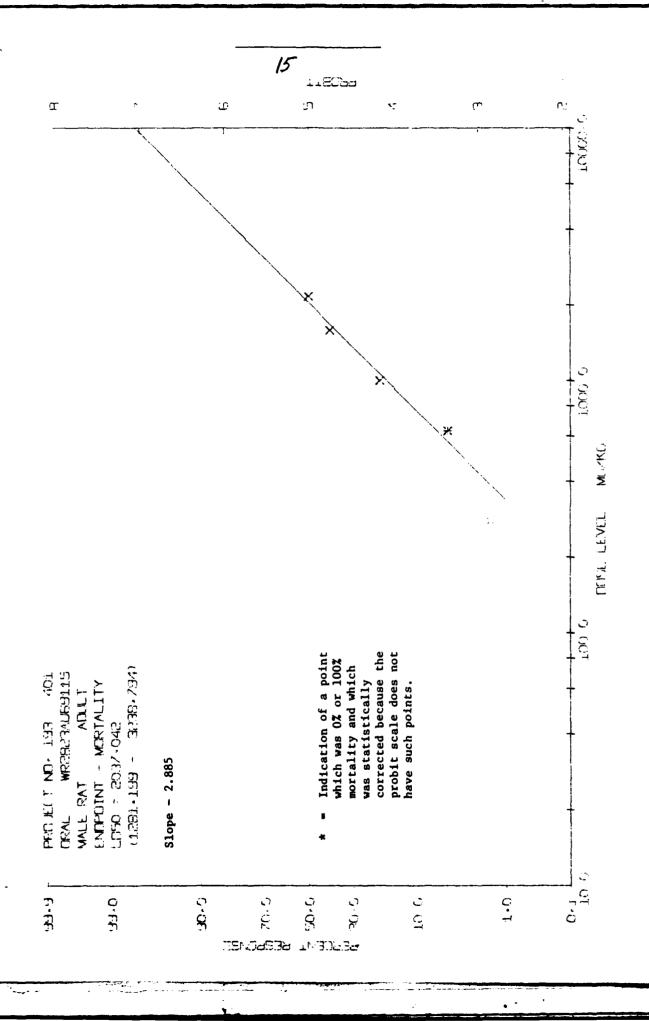
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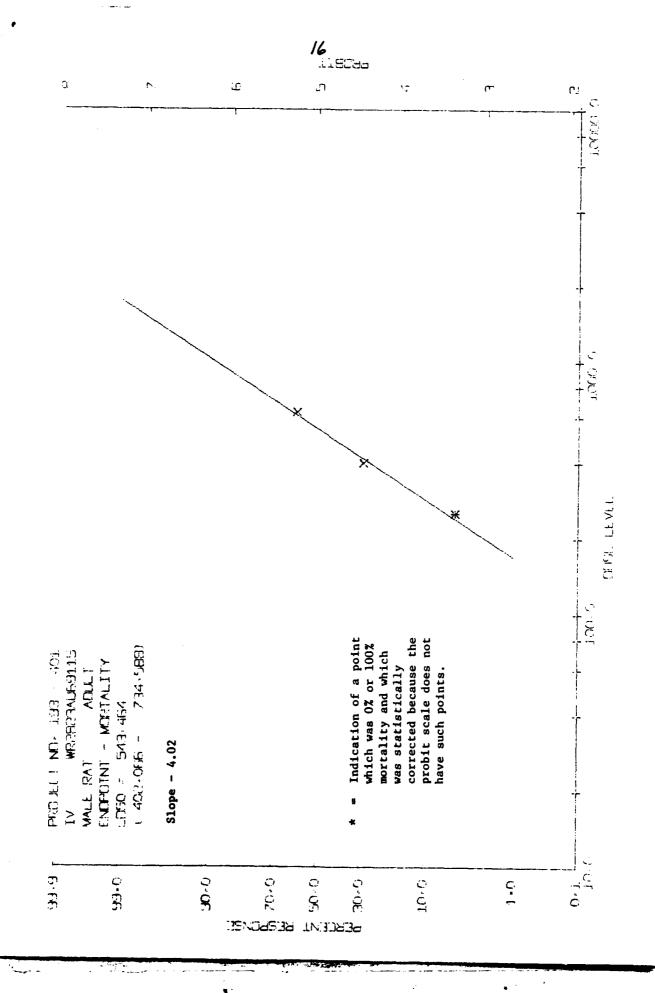
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Report Preparation: Lambert

Supervision: Fink

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#### HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: September 11, 1969

Material:

WR-2823 (AU 69115)

Subject:

FINAL REPORT

Acute Oral and Intraperitoneal Toxicity Studies - Mice

Project No. 193-402

#### SUMMARY

Acute oral and intraperitoneal toxicity studies were conducted in adult male albino mice using WR-2823 (AU 69115) as the test material. The acute oral LD $_{50}$  of WR-2823 was 374 mg/kg of body weight (confidence limits, 263 to 531 mg/kg of body weight), and the acute intraperitoneal LD $_{50}$  was 580 mg/kg of body weight (confidence limits, 449 to 750 mg/kg of body weight).

## MATERIAL

Date Received July 2, 1969.

Description White powder with no noticeable odor.

Purity Assumed to be 100% active ingredient.

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#### PROCEDURES

- Animals Seven groups (oral) and seven groups (intraperitoneal), each composed of 10 adult male albino mice of the Carbia strain, weighing from 16 to 29 grams.
- <u>Drug Administration</u> The test material was administered by gastric intubation (six groups) or intraperitoneal injection (six groups) as a 0.5%, 1%, or 2% weight-per-volume solution in saline. The control, saline, was administered by gastric intubation to one group at a dosage level of 1000 mg/kg of body weight and by intraperitoneal injection to one group at a dosage level of 631 mg/kg of body weight.

#### Dosage Levels

Oral: 100, 159, 251, 398, 631, and 1000 mg/kg of body weight.

Intraperitoneal: 63.1, 100, 159, 251, 398, and 631 mg/kg of body weight.

- Observations For mortality and pharmacotoxic effects immediately after dosing, frequently on the day of dosing, and daily thereafter for 14 days.
- Statistical Analysis Mortality data were analyzed by the method of Litchfield, J. T., and Wilcoxon, F., J. Pharmacol. Exptl. Therap. 96, 99, 1949, or Finney, D. J., Probit Analysis, Cambridge University Press, 1952.

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RESULTS

Mortality Data Values below represent the number of animals dead per number of animals tested, cumulative.

Oral:

	Concentration		Time of	Death				
Dose	of Solution	Immediate	Hours		Da	iys		
mg/kg	7		1 4-24	2	3	4-5	6-7	8-14
100	1.0	0/10	0/10 0/10	0/10	1/10	2/10	2/10	3/10
159	1.0	0/10	0/10 0/10	0/10	0/10	0/10	0/10	0/10
251	1.0	0/10	0/10 0/10	0/10	0/10	0/10	0/10	1/10
398	1.0	0/10	0/10 0/10	1/10	2/10	3/10	4/10	5/10
631	2.0	0/10	2/10 4/10	6/10	8/10	8/10	8/10	8/10
1000	2.0	0/10	7/10 9/10	9/10	9/10	9/10	9/10	9/10

 $LD_{50}$ , mg/kg - 374

Confidence Limits (95%), mg/kg - 263 to 531

Slope - 2.353

Graphical presentation of the dose-response evaluation is appended to this report.

## Intraperitoneal:

	Concentration		Time of Death						
Dose	of Solution	Immediate	Hou	irs	Days				
mg/kg	7	•	1-4	24	2-7	8	9	10-14	
63.1	0.5	0/10	0/10	0/10	0/10	0/10	1/10	1/10*	
100	0.5	0/10	0/10	0/10	0/10	1/10	1/10	1/10*	
159	0.5	0/10	0/10	0/10 .	0/10	0/10	0/10	0/10	
251	1.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	
398	1.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	
631	1.0	0/10	3/10	5/10	6/10	6/10	6/10	6/10	

 $LD_{50}$ , mg/kg - 580

Confidence Limits (95%), mg/kg - 449 to 750

Slope - 8.960

Graphical presentation of the dose-response evaluation is appended to this report.

\* The deaths which occurred at these levels on Day 8 and Day 9 were considered incidental deaths and were not used in  ${\rm LD}_{50}$  calculations.

## Principal Toxic Effects

Following Oral Administration:

Control Group - One animal died on Day 9 with death preceded by labored respiration, prostration, and salivation.

Test Groups -

(100, 159, and 251 mg/kg Levels) Slight depression was noted immediately or at one hour for all animals with piloerection and hunched appearance noted later in the study. Three deaths occurred by Day 10 at the 100 mg/kg level, and one death occurred by Day 11 at

- the 251 mg/kg level. Surviving animals appeared normal by Day 6 (100 and 159 mg/kg level) or Day 13 (251 mg/kg level).
- (398, 631, and 1000 mg/kg Levels) Animals exhibited depression and labored respiration immediately or one hour after administration of the compound. Signs noted later in the study included ptosis, cold to touch, piloerection, hunched appearance (631 and 1000 mg/kg levels), urine stains (398 mg/kg level), and brown stains on body (398 mg/kg level). One animal at the 631 mg/kg level showed tremors at 48 hours. Five deaths occurred at the 398 mg/kg level by Day 11, eight deaths occurred by Day 3 at the 631 mg/kg level, and nine deaths occurred by four hours at the 1000 mg/kg level. Survivors at these levels appeared normal on Day 14.

#### Following Intraperitoneal Administration:

- Control Group Slight depression was noted immediately after administration of the compound. One death occurred in this group on Day 9.

  Test Groups -
  - (63.1 and 100 mg/kg Levels) Animals exhibited slight depression immediately or one hour after administration of the compound through four hours. One death occurred on Day 9 at the 63.1 mg/kg level, and one death occurred on Day 8 at the 100 mg/kg level.
  - (159, 251, 398, and 631 mg/kg Levels) All animals exhibited slight depression immediately after administration of the compound. Toxic

signs noted later in the study included labored respiration, ptosis (three higher levels), piloerection (159 and 631 mg/kg levels), urine stains (three higher levels), squinted eyes (159 and 631 mg/kg levels), slight ataxia (two higher levels), cold to touch (two higher levels), and hunched appearance (631 mg/kg level). Animals at the 159, 251, and 398 mg/kg levels appeared normal by Day 6. Six deaths occurred at the 631 mg/kg level by Day 3 with survivors appearing normal by Day 12.

## Major Necropsy Findings

Following Oral Administration:

At Death -

(Control) No necropsy could be performed on the animal which died due to advanced autolysis and cannibalization of the animal.

(Test Groups) Necropsies were not performed on one animal at the 100 mg/kg level and on two animals at the 398 mg/kg level due to cannibalization. One necropsy at the 251 mg/kg level and one at the 398 mg/kg level were not performed due to advanced autolysis. Gross pathology noted included stomach thin and smooth (100 mg/kg level), stomach distended with yellow fluid or food-like material (100, 398, 631, and 1000 mg/kg levels), intestines filled with yellow fluid (398 mg/kg level), red areas on intestinal walls (398 mg/kg level), liver dark reddish brown in color (100 mg/kg level), liver pale red in color (398 mg/kg level), margins of liver transulcent in appearance (631 mg/kg level), kidneys dark

red in color (100 and 1000 mg/kg levels), poor differentiation between cortex and medulla of kidneys (100, 398, 631, and 1000 mg/kg levels), and margins of cut surface of kidneys translucent in appearance (1000 mg/kg level).

At Sacrifice - No observable gross pathology in either control or test groups. Following Intraperitoneal Administration:

At Death -

(Control) No necropsy was performed on the one animal which died in this group due to cannibalization of the animal.

(Test Groups) Necropsies were not performed on one animal at the 63.1 mg/kg level, on one animal at the 100 mg/kg level, and on one animal at the 631 mg/kg level due to cannibalization of the animals. Gross alterations, all noted at the 631 mg/kg level, included clear fluid in peritoneal cavity, margins of liver translucent in appearance, dark red kidneys, and poor differentiation between cortex and medulla of kidneys.

At Sacrifice - No observable gross pathology in either control or test groups.

Submitted by

MARCELINA B. POWERS, D.V.M., M.S.

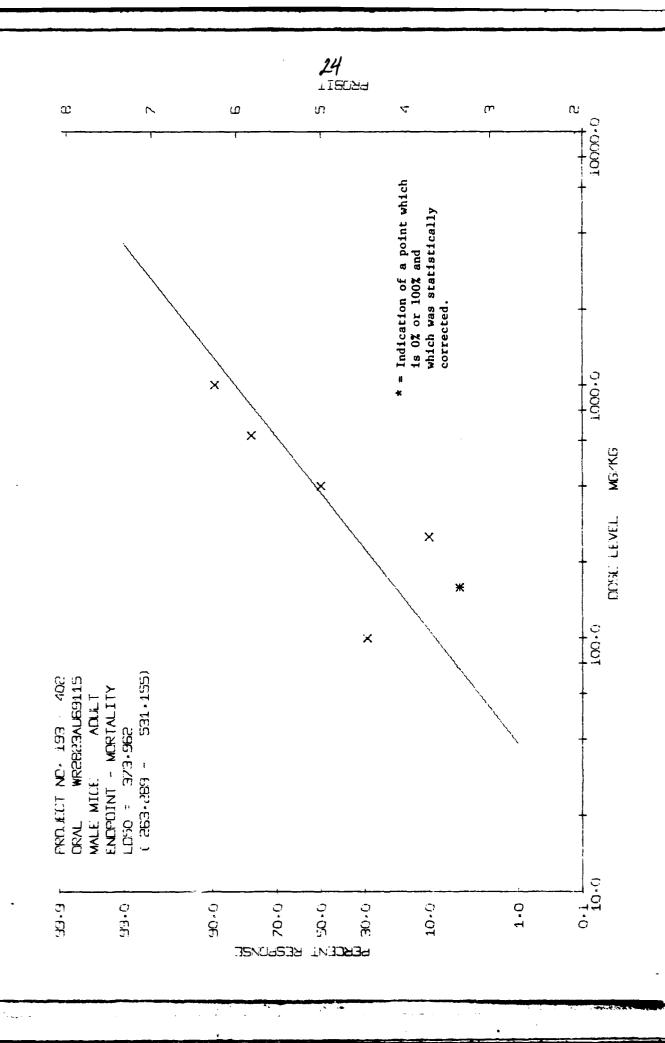
Project Manager, Drugs and Industrial Chemicals

Toxicology-Biosciences Laboratory

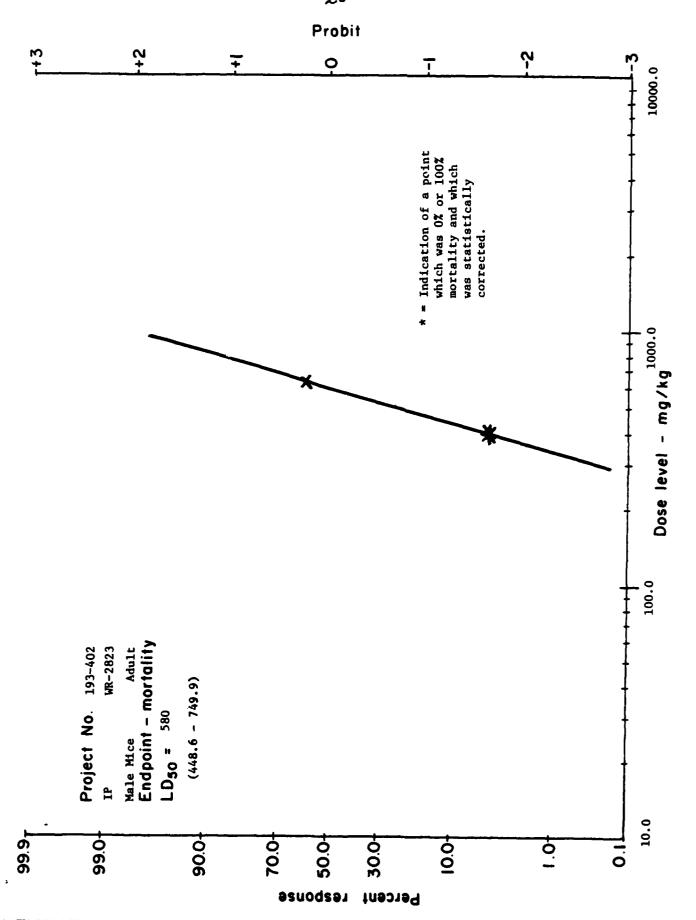
Report Preparation: Lambert

Supervision: Minner

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#### HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: September 18, 1969

Material: WR-2823 (AU 69115)

Subject: FINAL REPORT

Acute Oral and Intraperitoneal Toxicity Studies - Guinea Pigs

Project No. 193-403

#### SUMMARY

Acute oral and intraperitoneal toxicity studies were conducted in adult male albino guinea pigs using WR-2823 (AU 69115) as the test material. The acute oral  ${\rm LD}_{50}$  in guinea pigs obtained for the compound was 800 mg/kg of body weight (confidence limits, 360 to 1778 mg/kg of body weight), and the acute intraperitoneal  ${\rm LD}_{50}$  was 272 mg/kg of body weight (confidence limits, 185 to 400 mg/kg of body weight).

#### MATERIAL

Receipt Date July 2, 1969.

Description White powder with no noticeable odor.

Purity Assumed to be 100% active ingredient.

#### **PROCEDURES**

- Animals Five groups of 10 adult male albino guinea pigs (Camm strain) and two groups of five adult male albino guinea pigs for the oral administration and seven groups of 10 adult male albino guinea pigs for the intraperitoneal administration. The animals weighed from 226 to 412 grams.
- Drug Administration The test material was administered by gastric intubation (four groups of 10 animals and two groups of five animals) or intraperitoneal injection (six groups of 10 animals) as a 1% or 10% weight-per-volume solution. The control, saline, was administered by gastric intubation to one group of 10 animals at a dosage level of 1000 mg/kg and by intraperitoneal injection to one group of 10 animals at a dosage level of 631 mg/kg.

#### Dosage Levels

Oral: 100, 159, 251, 398, 631, and 1000 mg/kg of body weight.

Intraperitoneal: 63.1, 100, 159, 251, 398, and 631 mg/kg of body weight.

- Observations For mortality and pharmacotoxic effects immediately after dosing, frequently on the day of administration, and daily thereafter for 14 days.
- Statistical Analysis Mortality data was analyzed by the method of Finney, D. J.,
  Probit Analysis, Cambridge University Press, 1952.

#### RESULTS

Mortality Data Values below represent the number of animals dead per number of animals tested, cumulative.

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## Oral:

Concentration		Time of Death								
Dose	of Solution	Immediate		Hours				Days		
mg/kg	7		1	4	24	2-3	4	5	6	7-14
100	10	0/10	0/10	0/10	0/10	0/10	0/10	1/10	1/10	1/10
159	10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
251	10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10	1/10
398	10	0/10	0/10	2/10	2/10	2/10	2/10	2/10	2/10	2/10
631	10	0/5	1/5	1/5	2/5	2/5	3/5	3/5	3/5	3/5
1000	10	0/5	1/5	1/5	2/5	2/5	3/5	3/5	3/5	3/5

 $LD_{50}$ , mg/kg - 800

Confidence Limits (95%), mg/kg - 360 to 1778

Slope - 1.942

Graphical presentation of the dose-response evaluation is appended to this report.

#### Intraperitoneal:

	Concentration of Solution	Time of Death							
Dose		Immediate	Hours			Days			
mg/kg	*		1	4	24	2-3	4-11	12	13-14
63.1	1.0	0/10	0/10	0/10	0/10	1/10	1/10	1/10	2/10
100	1.0	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
159	10.0	0/10	0/10	0/10	0/10	0/10	0/10	1/10	1/10
251	10.0	0/10	2/10	6/10	6/10	6/10	6/10	6/10	6/10
398	10.0	0/10	8/10	8/10	8/10	8/10	8/10	8/10	8/10
631	10.0	0/10	7/10	7/10	7/10	7/10	7/10	7/10	7/10

 $LD_{50}$ , mg/kg - 272

Confidence Limits (95%), mg/kg - 185 to 400

Slope - 2.196

Graphical presentation of the dose-response evaluation is appended to this report.

## Principal Toxic Fefects

Following Oral Administration:

Control Group - Slight depression was noted immediately after administration.

Test Groups -

(100, 159, and 251 mg/kg Levels) All animals exhibited slight depression immediately after administration of the compound through 48 hours. One animal at the 251 mg/kg level exhibited labored respiration immediately after administration of the compound through four hours, and one animal had a swollen right hindleg from Day 5 through termination of the study.

(398, 631, and 1000 mg/kg Levels) Depression and labored respiration were noted in all animals immediately after compound administration. Toxic signs noted later in the study included comatose appearance (two animals at the 398 mg/kg level and one animal at the 631 mg/kg level), squinting (631 and 1000 mg/kg levels), lacrimation (631 and 1000 mg/kg levels), hunched appearance (631 and 1000 mg/kg levels), ptosis (1000 mg/kg level), convulsive jerking (one animal at the 1000 mg/kg level). Two deaths occurred at the 398 mg/kg level by four hours, three deaths occurred at the 631 mg/kg level by Day 4, and three deaths occurred at the 1000 mg/kg level by Day 5. Surviving animals at these levels appeared normal by Day 5 or Day 8.

#### Following Intraperitoneal Administration:

Control Group - One death occurred on Day 4 preceded by an apparent prolapsed intestine; all other animals appeared normal.

#### Test Groups -

(63.1 and 100 mg/kg Levels) Depression was noted in all animals immediately after administration of the compound through four hours. One death occurred on Day 3 and one on Day 11 at the 63.1 mg/kg level.

- (159 mg/kg Level) Depression and slow, labored respiration were noted one hour after administration of the compound with lacrimation noted later in the study. Animals appeared normal by Day 4 with one death occurring on Day 12 (no toxic signs noted preceding death).
- (251, 398, and 631 mg/kg Levels) All animals exhibited depression immediately after administration and labored respiration immediately or one hour after administration. Delayed toxic signs included squinting (251 and 631 mg/kg levels), lacrimation (398 and 631 mg/kg levels), ptosis (398 and 631 mg/kg levels), comatose appearance (one animal at the 251 mg/kg level), and apparent weight loss (one animal at the 631 mg/kg level). Six deaths occurred at the 251 mg/kg level by four hours. Eight deaths at the 396 mg/kg level and seven deaths at the 631 mg/kg level occurred by one hour. Signs subsided in surviving animals at the 251 and 398 mg/kg levels by Day 4 and at the 631 mg/kg level by Day 7.

#### Major Necropsy Findings

Following Oral Administration:

At Death -

(Test Groups) No necropsy was performed on the animal which died at the 100 mg/kg level due to advanced autolysis and cannibalism of the animal. Gross pathology observed in other animals included: stomach lining dark red (251, 631, and 1000 mg/kg levels), stomach distended with clear fluid

resembling compound (398 mg/kg level), stomach lining blanched (398 mg/kg level), stomach walls thin (631 and 1000 mg/kg levels), renal medulla dark pink (251 mg/kg level), poor differentiation between cortex and medulla of kidneys (398, 631, and 1000 mg/kg levels), kidneys dark red in color (631 and 1000 mg/kg levels), liver surface mottled (398 mg/kg level), and liver dark reddish brown in color (631 and 1000 mg/kg levels).

#### At Sacrifice -

(Control) No observable gross pathology.

(Test Groups) Blanched areas in stomach (631 mg/kg level) and liver dark reddish brown (631 mg/kg level).

#### Following Intraperitoneal Administration:

#### At Death -

(Control) Intestines greatly distended (one animal).

(Test Groups) Lungs distended with yellow abscessed areas (63.1 mg/kg level), lungs distended and dark red in color with lobes adhered to each other (63.1 mg/kg level), thoracic cavity filled with dark red fluid (63.1 mg/kg level), peritoneal cavity filled with clear fluid resembling compound (251, 398, and 631 mg/kg levels), poor differentiation between cortex and medulla of kidneys (251, 398, and 631 mg/kg levels), and liver dark reddish brown in color (251, 398, and 631 mg/kg levels).

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At Sacrifice -

(Control) No observable gross pathology.

(Test Groups) No observable gross pathology.

Submitted by

INA B. POWERS, D.V.M., M.S.

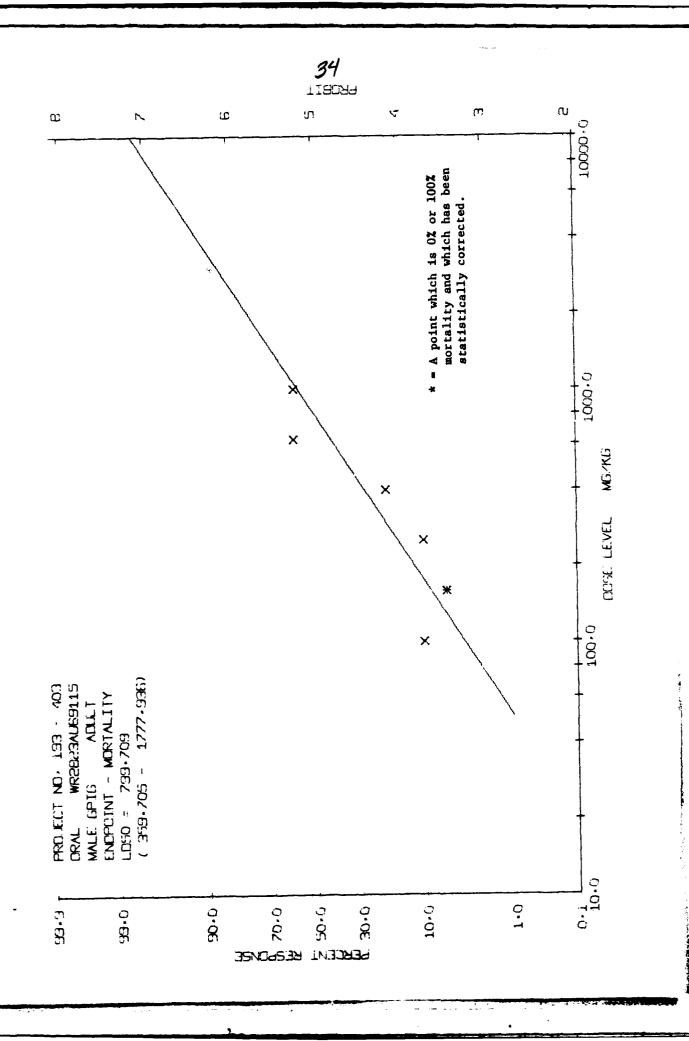
Project Manager, Drugs and Industrial Chemicals

Toxicology-Biosciences Laboratory

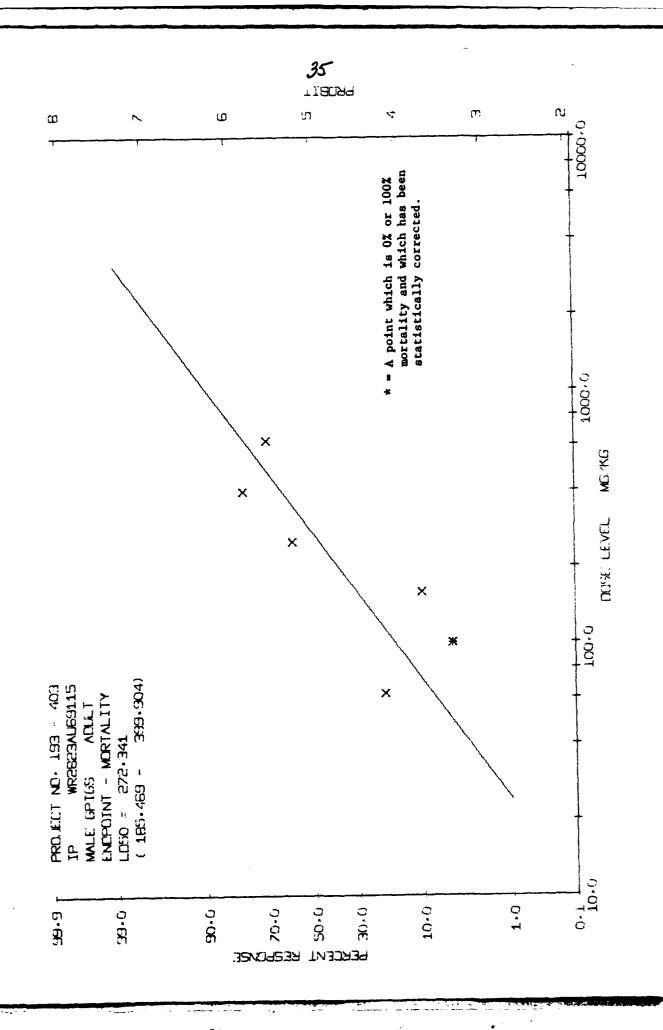
Report Preparation: Lambert

Supervision: Fink

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#### HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: January 23, 1970

Material: WR-2823 (AU 69115)

Subject: REPORT NO. 31

Two-Week Intravenous Toxicity Study - Rats

Project No. 193-404

#### SUMMARY OF FINDINGS

This study was conducted to evaluate and characterize the effects of short-term intravenous administration of WR-2823 (AU 69115) in male and female albino rats. The test material was administered daily for 15 days at dosage levels of 30, 60, 120, and 15 mg/kg/day.

Criteria evaluated for compound effect were physical appearance and behavior, body weight gains, food consumption, survival, clinical laboratory results, and gross findings at necropsy.

The following signs were observed in the test rats after the daily dose: marked or slight depression; squinted eyes; lacrimation or watery eyes. The degree and frequency of these signs decreased at each lower dosage level. Salivation after the dose was noted only occasionally, most frequently in the high level test rats.

Growth and food consumption for the test rats were generally comparable with those for the controls. Except for somewhat higher blood sugar values obtained for the male and female test groups at one and two weeks, the results of the clinical values for the test groups were generally comparable with those for the controls.

At necropsy the following observations were made in test rats only: apparent thickening of the wall of the small intestine (eight test rats); small, yellow foci on the duodenal lining (seven test rats); a thickened-appearing stomach wall (three rats from Groups No. 3 and No. 4); and a rough-appearing lining of the nonglandular portion of the stomach (one rat in Group No. 4).

The preserved tissues were not examined microscopically.

#### MATERIAL

<u>Identification</u> WR-2823 (AU 69115); S-2-(5 aminopenylamino) ethylphosphorothoic acid monohydrate.

Description A fine, white powder; no odor noted.

Receipt From Walter Reed Army Institute of Research on July 2, 1969.

Purity Considered 100% active ingredient.

#### **METHODS**

#### Experimental Animals

One hundred young albino rats, 50 males and 50 females, of the Charles River Caesarean-derived strain.

Weight Range at Initiation: For the males from 207 to 247 grams and for the females from 185 to 231 grams.

Housing: Individually in elevated wire mesh cages.

Diet: Purina Laboratory Chow and water available ad libitum.

# Animal Groups and Dosage Levels

Method of Grouping: Stratified randomization.

Group No.	No. of	Animals female	Dosage Levels mg/kg/day
1 (vehicle control)	10	10	0
2	10	10	30
3	10	10	60
4	10	10	120
5	10	10	15

# Preparation of Solutions

Vehicle: 0.9% Sterile Saline.

Concentrations: 30, 60, 120, and 15 mg. of the test compound per milliliter of vehicle for Groups No. 2, No. 3, No. 4, and No. 5, respectively.

The compound jar was kept in the freezer within a second container; the jar was warmed to room temperature before preparation of the daily solutions.

### Drug Administration

Each test rat received a daily intravenous injection via the lateral tail vein of the test compound at the required dosage level as a freshly prepared solution at a volume of 0.1 ml. per 100 grams of body weight. Dosages

were adjusted on the basis of individual body weights. Control rats received equivalent volumes of the vehicle.

The first five rats in each group received 16 injections, and the last five in each group received 15 injections. All rats were sacrificed on the day following the last dosage; no dosages were administered on the day of sacrifice.

### Observations and Records

Daily Observations: For appearance, behavior, and mortality.

Daily Observations and Records: Individual body weights and dosages; appearance and behavior of each rat prior to dosage and signs of toxic and/or pharmacologic effects after dosage.

Weekly Records: Individual weekly food consumption.

### Clinical Laboratory Studies

Intervals: Initially, at one week, and two weeks (terminal).

Method: Performed on five rats from each group; blood samples were obtained from the tail vein (from the abdominal aorta for biochemical studies at sacrifice). Urine samples were collected from rats housed overnight in individual metabolism cages and pooled by groups.

Hematology: Erythrocyte count; total and differential leukocyte counts; microhematocrit, hemoglobin, and prothrombin and coagulation time determinations.

Biochemistry: Fasting blood sugar, blood urea nitrogen, serum glutamicpyruvic transaminase, and alkaline phosphatase determinations. Urine Analyses: Appearance, pH, specific gravity, sugar acetone, protein, bilirubin, occult blood, and microscopic examination of the sediment.

## Ophthalmologic Examinations

Conducted on all rats assigned to the study initially and at termination, prior to sacrifice, using "Mydriacyl" (Alcon) and a binocular indirect ophthalmoscope.

### Terminal Studies

Terminal Sacrifice: Performed on each rat one day after the last injection (the 15th or 16th dose).

Method - Exsanguination under Diabutal anesthesia.

Gross Observations - Recorded at necropsy for each rat.

Organ Weights (Determined for Each Rat) - Liver, kidney, spleen, heart, testes with epididymis, and ovaries - prior to fixation; thyroid and adrenals - after fixation.

Tissues Preserved From Each Rat -

(In 10% Neutral Buffered Formalin) Brain, pituitary, spinal cord (three levels), thyroid, lung, heart, liver, spleen, kidney, adrenal, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testis, prostate, ovary, uterus, bone, bone marrow, and unusual lesions.

(In Alcoholic Formalin) Eyes.

No tissues were examined microscopically.

All tissues are being held at Hazleton Laboratories, Inc., for possible future reference.

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#### RESULTS

### Gross Appearance and Behavior

Transient wheezing and a swollen left eyelid were noted each in one male control rat; staining of the abdominal fur by urine was observed on Days 4 - 16 in another control male. The remaining male control animals and all control females had a normal appearance.

Wheezing, nasal discharge, red eyelid, urine stains on the abdominal fur, or alopecia on the body were noted in a few rats in the various test groups before the daily dose. Seven female test rats, one or two from each test group, developed a yellow discoloration of the furcoat first noted toward the end of the first experimental week and observed daily until sacrifice. Most of the rats, however, appeared normal prior to treatment.

Depression following injection was observed daily in all animals in Groups No. 4 and No. 3 (120 mg/kg and 60 mg/kg, respectively). Slight depression was observed daily in the majority of the test rats in Group No. 2 (30 mg/kg) and less frequently in Group No. 5 test rats (15 mg/kg).

Squinted eyes following treatment were observed daily in almost all rats in Group No. 4, less frequently in the animals in Group No. 3, and only once in one female in Group No. 2.

Lacrimation or watery eyes were noted daily after treatment in numerous high level rats and less frequently at each lower test level.

Salivation after the dose was observed occasionally in several animals in the various test groups, the frequency being highest in the high level group.

# Growth, Food Consumption, and Survival

Mean weekly body weight and food consumption data are presented below.

TABLE NO. 1
Mean Weekly Body Weights and Food Consumption

					Ma	ıle				
<u>Week</u>	Group Weight	No. 1 Food Cons.	Group Weight	No. 2 Food Cons.	Weight	No. 3 Food Cons.		No. 4 Food Cons.	Weight	No. 5 Food Cons
	g.	g.	g.	8.	g.	g.	g.	g.	g.	g.
0	231	-	226	-	223	-	231	-	229	-
1	277	144	268	150	261	137	256	113	276	148
2	315	151	306	159	296	158	284	152	316	160
					Fer	nale				
	Group	No. 1	Group	No. 2	Group	No. 3	Group	No. 4	Group	No. 5
Week	Weight	Food Cons.	Weight	Food Cons.	Weight	Food Cons.	Weight	Food Cons.	Weight	Food Cons
	g.	g.	g.	g.	g.	g.	g.	g.	g.	g.
0	209	-	212	-	205	-	206	-	205	-
1	229	130	230	114	229	109	232	110	222	116
2	248	131	245	122	245	136	255	141	239	124

Weight gains and food consumption for the high level males (Group No. 4 - 120 mg/kg) were slightly lower compared with those for the male control and the remaining male test groups. Body weight gain and food consumption were comparable among the female control and test groups. Survival was 100%.

# Results of Ophthalmoscopic Examination

Gross ophthalmoscopic examination performed on all rats in this study at initiation and prior to sacrifice revealed no gross eye abnormalities in any of the animals.

## Clinical Laboratory Studies

The hematological values determined at one and two weeks for the male and female test groups showed no significant differences from control values, and no dose-related trends were apparent. At one week, all mean values for the test groups were comparable with those for the respective control groups. At two weeks, the group means for hematocrit and hemoglobin for the high level female group (Group No. 4 - 120 mg/kg/day) were lower than the respective control values due to abnormally decreased values for one high level female (Rat No. 82-766, one of the rats that had showed a yellow discoloration of the fur during the second week of the study). At two weeks, the percent of segmented neutrophils in female Group No. 4 was somewhat elevated. Except for a few decreased or elevated individual values obtained for control and test rats, all remaining values were within normal limits and comparable among the test and control groups.

A slight trend toward higher blood sugar values was evident at one week in the male and female test groups, but all values were within normal range. The two-week blood sugar values showed an overall increase in all groups including the controls and were highest for both sexes at the high test level, but only a few individual values were above the normal range for laboratory rats.

The mean alkaline phosphstase values for the test groups were also somewhat higher than the respective control values, but no dose-related trend

was evident. The other biochemical values and the results of urine analyses were within normal range and comparable among the test and the respective control groups.

## Gross Observations at Necropsy

The following gross alterations were observed in several test rats only:

A thickened-appearing wall of the small intestine (mostly the duodenum) in one of 10 males in Group No. 2 - 30 mg/kg; in one male and two females in Group No. 3 - 60 mg/kg; and in one male and three females in Group No. 4 - 120 mg/kg. The lining of the duodenum in the above rats in Groups No. 3 and No. 4 showed small, yellow foci.

A thickened-appearing stomach wall in one male in Group No. 3 and in two females in Group No. 4; in addition, a rough-appearing lining of the nongrandular portion of the stomach in a third female in Group No. 4. Similar findings in stomach or small intestine were not observed in the low level test group (15 mg/kg - Group No. 5).

Slight to moderate enlargement of the spleen was noted in four of 10 male control rats, in two males and two females in Group No. 2, one male in Group No. 3, one female in Group No. 4, and two males and one female in Group No. 5. The weights of the above enlarged-appearing spleens ranged from 1.00 to 1.57 grams. These weights are slightly higher than those usually found in young laboratory rats.

Gross alterations in the lung noted in two control male rats, in three 30 mg/kg rats, seven 60 mg/kg rats, seven 120 mg/kg rats, and four 15 mg/kg rats included small, consolidated or abscessed areas; small, gray, cyst-like areas; distension of the lobes, or dark red areas in the lobes. The dark red areas were apparently caused by aspiration of blood at sacrifice.

Findings in the liver included small, yellow foci in the left lateral lobe (one control male); a small, firm, yellow area in the median lobe of the liver (one 60 mg/kg male), a pale yellow-brown discoloration of the liver and/or thickened liver lobes (in one 60 mg/kg and two 120 mg/kg animals).

A control male had a dilated renal pelvis. Eight test rats at various levels showed one or several of the following kidney alterations: both pelves dilated; a greenish or pale yellow-brown kidney cortex; a dark pink outer medulla; or a speckled surface.

A dark red cyst surrounding the left ovary was found in one control female. The uterine horns of one control and several test rats at various test levels were distended with clear fluid.

Two females (Groups No. 3 and No. 4) had severe alopecia on the body; sections of skin were preserved.

Female Rat No. 82-786 (15 mg/kg - Group No. 4) had a dark pink, rough, thickened bladder wall; the bladder contained numerous calculi from small granules to firm, white stones, measuring approximately 1.0 x 5.0 cm. in diameter. Both renal pelves were dilated and contained small, firm granules.

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# Microscopic Analyses

At the request of the project officer, no histopathological examination of the tissues was performed. All preserved tissues are being held at Hazleton Laboratories, Inc., for possible future reference.

Submitted by

MARCELINA B. POWERS, D.V.M., M.S

Project Manager, Drugs and Industrial Chemicals

Toxicology-Biosciences Laboratory

Report Preparation: T. Kundzin

Supervision: Fink

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# EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

- T = trace (±)
- 0 = negative
- 1 = slight (+)
- 2 = moderate (++)
- 3 = marked (+++)
- 4 = severe (++++)

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINU RATS RECEIVING WR-2823 FOR THO HEEKS INITIAL

		S					1		0.1555	DIFFERENTIA	1		
GROUP NUMBER	AN IHAL MUMRER	ш×	HCT %	HGB	RBC MILLS	WBC	META %	BAND	SEG %	LYMPH	MONO %	EOSI %	BASO
-	82696	Σ	45.0	-		-	0	c	10	æ	^	c	c
	82697	Σ	Ø	3	•	~	c	· c	-	9	J -	c	> <
_	82698	Σ	୯	3		; ;	. ~		21	0 K	<b>-</b> -	<b>:</b> r	<b>=</b> 0
~	82699	Σ	~	6	•		٠ ح	• <	17	0.2	° (	٠,	= (
-	82700		41.0	12.2	6.27	17.5	C	0	12	83	n m	- ر	<b>-</b>
GROUP	MEAN		43.0	12.9	6.47	16.0							
~	82716	Σ	46.0	13.2	6.74	S.	0		15	84	-	C	_
7	82717		38.0	2	5.78	7	С		10	06	• •	: c	٠
~	82718		41.0	2	6.04	3.	0		19	8.3	c <b>c</b>	: c	<b>:</b> c
~	82719		45.0	4	6.40	-	c	0	21	78	· c	) <del>-</del>	= =
^	82720		45.0	3	6.85	13,3	C	c -	0.8	36	0	· c	) C
GROUP A	MEAN		43.0	13.0	6.36	15.6							
ю	82736	Σ	50.0	2	6.59		c	C	26	74	c	c	c
m	82737	Σ	40.0	2	6.31	9	C	^	7	78		: C	•
۳	82738	Σ	48.0	14.0	96.9	S	С	; C	23	7.2	÷ c	÷ c	<b>-</b>
æ	82739	Σ	48.0	3	68.9	6	0	· C	17	- 6	,	c <b>c</b>	<b>-</b>
6	82740	Σ	49.0	4	7.70	12.6	С	c	25	75	0	; c	<b>-</b> -
GROUP F	MEAN		47.0	13.5	68.9	15.0							
4	82756	Σ	41.0	~	6.35	-	0	-	24	75	c	c	c
4	82757	Σ	44.0	7	69.9	æ	0	· -	. ~	70	o c	: ^	- 0
4	82758	Σ	43.0	C	6.77	2	C	۰	2,4	- 62	c	ં (	5 6
4	82759	Σ	38.0	~	60.9	, 5	· =		2 6	n a			= =
4	82760	Σ	45.0	12.6	6.55	18.5	c	<b>+</b> C	202	79	00		၁၁
GROUP MEAN	1EAN		41.6	12.6	64.9	15.8							

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS INITIAL

1 1 1	BAS⊓ %	c	С	C	0	~	٠.
1 1	E051N	-	-	<b>∼</b>	_	C	
1	MONO %	ù	0	C		0	
RENTIAL	META BAND SEG LYMPH MONO EOS	73	72	84	76	80	
PIFFE	SEG %	25	56	14	22	20	
1	BAND %	c	-	C	0	o,	
 	META %	C	C	0	С	ć	
	WBC THS					18.0	
	RBC MILLS	6.58	6.04	6.51	6.63	6.63	6.48
	HGB 64	13.4	12.0	12.6	13.4	12.7	12.8
	HC #	47.0	45.0	41.0	46.0	44.0	44.0
S	ш×	Σ	Σ	Σ	Σ	Σ	
	AN I MAL NUMBER	82776	82777	82778	82779	82780	4E AN
	GROUP	ις	Ŋ	'n	īC	S	GROUP MEAN

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WFEKS WEEK 1

		S					1		DIFFE	DIFFERENTIAL	!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!	1 1 1	1
GROUP NUMBER	ANIMAL	шх	HCT %	F # 5	RBC MILLS	WBC	KETA %	BAND %	SEG %	ГУМРН %	MONO %	EOSIN %	RASO %
_	82696	Σ	7	C	C	28.6	c	0	4	92	0	4	0
-	82697	Σ	$\infty$	4	2	11.9	0	0	13	86	_	C	0
_	85698	Σ	43.0		•	12.2	0	0	56	7.1	2		0
_	82699	I	G	~	3	20.6	0	0	11	86	2	-	0
-	82700	Σ	2	13.0	6.17	16.3	O	0	21	42	~	4	0
бкопр	MEAN		44.6	13.5	6.23	17.9			75				
7	82716		3	~	60.9	æ	0	С	10	06	0	c	С
~	82717		~	3	6.07	æ	C	С	15	84	0	7	С
~	82718	Σ	45.0	12.6	00.9	16.6	0	0	6	89	-	_	0
~	82719		2	3	6.39	8	0	0	œ	91		c	0
~	<b>8272</b> 0		5	3	8.49	8	С	0	27	73	0	c	0
GROUP	MEAN		43.8	13.0	19*9	20.0							
m	82736		50.0	4	5	-	c	0	21	62	0	C	0
m	82737		46.0	n	3	5	C	0	7	93	0	C	С
ĸ	82738		48.0	S	S	1.	0	0	4	95	0	J	0
æ	82739	Σ	47.0	n		3.	0	c	Ś	95	0	c	0
m	82740		47.0	14.0	7.24	12.5	С	С	13	86	-	C	0
GROUP	MEAN		48.2	13.6	69.99	18.9							
4	82756		44.0	•	6.61	•	0	С	22	78	0	C	0
4	82757	Σ	48.0	14.2	6.77	24.2	C	C	10	06	0	c	C
4	82758		50.0	4	6.85	6	c	С	56	72	2	C	C
4	82759		44.0	•	6.34	5	C	С	18	82	С	C	C
4	82.760		48.0	4.	7.30	•	С	С	14	86	С	C	0
GROUP MEAN	MEAN		46.8	14.0	6.77	15.4			8				

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBIND RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

		S					1	111111	DIFFE	RENTIAL	1 1 1	1 1 1	1 1 1
OUP	SKOUP ANIMAL	u:	HCT	HGB	RUC	MBC	HETA	BAND	SEG	LYMPH	ONOW	EOSIN	BASO
UMBER	NUMBER	×	96	25	MILLS	THS	34€	₩	26	THS 25 24 25 25 25 25 25 25 25 25 25 25 25 25 25	℀	34	Ж
ĸ	82776	Σ	44.0	13.7	6.18	18.4	0	С	7	63	0	C	С
Ŋ	82777	I	0.04	11.5	6.08	13.8	0	0	15	85	c	C	င
Ŋ	82778	I	41.0	13.0	6.28	15.5	c	0	6	06	С	1	0
ß	82779	Σ	48.0	13.0	6.50	17.6	0	С	21	46	C	С	0
5	82780	I	44.0	13.0	6.42	24.5	С	С	12	87	7	O	0
OUP	GROUP MEAN		43.4	12.8	6.29	18.0							

TASEE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 2

		s.					1 1 1 1	11111	DIFFE	DIFFERENTIAL	1   1   1   1   1   1   1   1   1   1	111111	1
GROUP NUMBER	AN I MAL NUMBER		HCT ×	нен	RBC MILLS	WBC	META %	BAND	SEG *	LYMPH	MONO %	EOSIN %	RAS∩
-	82696		45.0	- 20	_	6	c	c	15	85	С	С	0
- ٠	4.2697		6.1.0	L	G	æ	c	¢	16	83	¢	<b>~</b>	C
	85958 82698		50.0	, 4	4	3	٥	0	20	79	0	-	C
۔ ہ	82699		45.0		S	δ.	0	c	œ	91	_	c	С
,i	82700	Σ	47.0	13.7	7.02	18.1	0	0	52	14	C	-	C
GROUP	MEAN		4.7.6	13.9	6.83	18.9							
^	82716		46.0	14.4	7.00	5	0	0	œ	62	С	c	C
1 0	82717	_	43.0	13.4	6.17	•	С	c	6	06	С	_	C
۸ د	82718	_	0.44	13.7	7.80	3	C	C	15	85	С	c	0
	82719		44.0	14.4	6.31	9	0	С	6	91	0	c	С
· ~	82720	Σ	51.0	15.0	7.32	14.3	С	C	19	81	c	C	0
GROUP	MEAN		45.6	14.2	6.92	17.1							
6	82736	_	46.0	60	7.24	7.6	0	c	16	84	0	C	0
· tr	82737	_	44.0	6	96.9	3	С	C	. 11	86	-	2	=
. 11	82738	_	50.0	15.0	7.36	22.7	С	С	11	88	С		С <sup>(</sup>
· w	82739	_	44.0	3.	6.26	_	С	0	9	94	0	C	C '
m	82740	Ξ	44.0	%	6.92	_	С	0	12	88 88	0	С	0
GRINDP	MEAN		45.6	13.6	6.95	17.7							
4	82756		44.0	13.	~	6	0	С	10	06	С	C	<b>C</b>
4	8275		45.0	12.	œ	<b>≈</b>	C	C	11	89	C	C	C :
4	8275E		44.0	13.	~	-	С	0	30	70	0	c ·	ο,
•	82759		44.0	12.	3	~	C	0	36	62	0	_	_
4	82760	Ξ. Ο	46.0	13.4	26.9	18.2	C	С	73	77	0	c	C
GROUP MEAN	MEAN		44.6	13.0	6.92	16.0							
:													

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 2

BASO	00000	;
	0 M C = 0	
MONO *	00000	
A BAND SEG LYMPH MOND EDSIN	83 77 80 78 90	
DIFFER SEG %	17 20 20 21 10	
BAND	00000	
META	00000	
WBC	16.0 17.1 16.1 14.6 23.6	17.5
RBC MILLS	7.24 6.39 6.58 7.00	6.94 17.5
HGB	14.6 12.6 12.7 13.5	13.4
HCT 32	46.0 42.0 45.0 45.0	44.2
νшх	ETTTT	
GROUP ANIMAL NUMBER NUMBER	82776 82777 82778 82779 82779	MEAN
GROUP NUMBER	กระบา	GROUP MEAN

TABLE NO. 2 - INDIVIDUAL HEHATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR THO WEEKS INITIAL

		s.					1 1	1	PEFF	DIEFERFNITAL	1 1 1	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	1
GROUP NUMBER	ANIMAL NUMBER	Ψ×	HC1	HGB GZ	RBC MILLS	WBC	META %	BAND %	SEG %	Г Умрн	ONOW		KAS∩ %
1	82706	ц.	48.0	4	7.47	6	C	0	2	2	c	c	c
_	82707		51.0	ွ	7.90		· C	· C	17	3 6	· c	- c	<b>.</b>
-	82708	ட	48.0	S	7-44	9	; c	; c	- α <u>.</u>	3 C	<b>-</b>	۲ ر	<b>&gt;</b> c
_	82709		51.0	•	7.31	, _	: =	· <b>-</b>		70	<b>•</b> •		<b>-</b>
-	82710		44.0	13.4	6.88	19.4	0	† C	19	79	co	-	-
GROUP	MEAN		48.4	14.4	7.40	18.1							
8	82726	u.	45.0	?		e.	С	1	15	83	-	C	C
7	82727		41.0	w.	6.58	7	0	0	=	986	ורר	· C	: <
~	82728		43.0	•	62.9	3	C	· c	: «	0 8	n	- -	<b>-</b>
7	82729	<b>L</b>	0.64	16.4	8,31	~	С	0	2 2 2	22	· -	o č	c c
~	я2730		45.0	æ	6.92	•	0	0	21	62	0	0	0
GROUP	MEAN		44.6	14.3	7.08	15.8							
m.	82746		42.0	ന	6.50	~		0	17	83	c	C	c
m	82747	u_	45.0	14.0	7.20		Ç	0	11	83	C	. –	: C
3	82748		43.0	n	6.60	-	0	0	15	85	: C	· c	; c
m	82749		48.0	す	7.18	5	0	0	56	02	: c	-	c
ĸ	82750		43.0	3	49.9	33	0	0	21	77	7	<b>-</b>	00
g(ii)	GROUP HEAN		43.6	13.4	6.82	13.3							
4	82766	u_	48.0	4	7.80	9	С	0	56	70	c	-	c
4	82767	u.	45.0	13.4	7.22	2	c	С	07	06		۰,	c
4	82768		46.0	4.	7.08	-	=	C	22	77	· c	- د	÷
4	82769		44.0	3	6.76	0	С	0	1,4	85	; <b>ç</b>	. –	: c
4	82770	ш	44.0	3	7.08	18.1	0	C	20	80	c	, C	c
(III)	GRAND MEAN		44.8	13.8	7.19	13.8							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS INITIAL

		S							JIFFE!	RENTIAL			1
SKTOP NUMBER	ANIMAL NUMBER	т×	HC #	HGB .>	RBC MILLS	WBC	META %	BAND %	SEG %	BAND SEG LYMPH MONO E	MON 0	EOSIM %	BASO %
יט	82786	u.	43.0	12.4	7.27	14.0	0	C	19	80	O	01	c
<u>د</u> ا	82787	ட	51.0	14.6	7.26	12.5	С	0	24	73	С	02	; <b>-</b> -
ır.	82788	щ	46.0	12.7	6.80	13,7	0	0	12	86		01	· c
بر ا	82789	u i	45.0	12.0	66.9	15.4	С	0	28	69	· C	; C	c
٠	82790	<b>u.</b> .	45.0	13.5	6.87	35.8	د	С	90	63	0	0.1	0
GROUP MEAN	MEAN		45.4	13.0	7.04	18.3							

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

GROUP NUMBER 1		)							コーニーコ コートボスドス コーニー		11111	1611111	1 1 1 1
	ANIMAL NUMBER	ш×	HCT %	нG В	RBC MILLS	WBC THS	META *	BAND %	SEG %	LYMPH	MONO %	EOSIN %	BASO %
-	82706	u_	45.0	14.0	6.81	4.	0	0	6	06	0		0
	82707	u.	50.0	14.6	6.19	6	С	C	59	70	C	_	С
_	82708	ட	44.0	14.2	8.07	7	0	0	12	85	0	'n	C
~	82709	u_	40.0	13.4	6.30	20.9	0	0	13	82	2	٣	0
_	82710	u_	44.0	14.6	6.64	12.9	С	0	12	87	0	1	0
GKOUP M	MEAN		44.6	14.2	6.92	15.9			75				
~	82728		44.0	14.4	9	4	C	0	18	80	С	~	0
~	82727		45.0	13.0	~	4	0	c	4	94	7	c	0
~	82728		44.0	14.6	3	4	0	0	13	85	0	~	0
7	82729	<u>u</u>	52.0	16.4	8.25	18.1	C	C	10	90	0	c	С
2	82.730		43.0	13.5	9	• 9	0	0	12	88	С	C	C
GROUP M	MEAN		45.0	14.4	6.88	17.7							
m	82746	u.	48.0	4		11.5	0	0	12	87	0	7	c
٣	82747	щ	44.0	4		13.0	0	0	· <b>9</b>	63	-	C	0
(C)	82748	ட	48.0	14.4	6.74	20.7	0	0	7	9.5	-	C	0
٣	82749	u_	0.64	5		15,1	0	0	6	91	C	С	0
60	82750	ட	45.0	œ.	•	14.1	c	0	13	87	c	c	0
я апия	MEAN		46.8	14.4	6.67	14.9							
4	82766		52.0	4	7.84	17.7	0	0	28	72	0	c	c
4	82767		45.0	3	6.38	10.8	С	C	16	80		^	C
4	82768		46.0	8	6.67	11.6	0	c	21	78	0		C
4	82769	u.	45.0	12.2	7.72	14.6	C	C	12	88	0	c	0
4	82770		44.0	2.	99•9	17.7	0	c	20	80	С	С	C
GROUP MEAN	IEAN		45.8	13.1	7.05	14.5			47				

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 1

v.					1 1	1 1 1 1 1	DIFFE	RENTIAL	1 1 1 1	1 1 1 1 1 1 1 1	1 1 1 1
ANIHAL E	H. H.	T HGB	RBC MILLS	WBC	META %	RAND %	SEG %	META BAND SEG LYMPH MONO FOSIN B/	MONO %	EOSIN %	_
82786 F			7.58	21.6	0	0	56	74	o	C	С
			6.80	11.6	C	0	22	76	-	-	
2788 F	44		6.95	17.6	0	0	7	93	c	c	
2789 6	444		6.72	11.3	0	C	11	85	-	m	
2790 F	45.0	13.7	6.51	53.1	C	c	æ	94	0	С	
	44.4	4 13.3	6.91	23.0							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

		S					1 1	!!!!!!!	DIFFE	DIFFERENTIAL			1
GROUP	AN I MAL NUMBER	шх	HCT %	нс в <b>сх</b>	RBC MILLS	WBC THS	META %	BAND %	SE6 %	LYMPH	WON 0	EDSIN %	BAS0
_	82706	4	45.0	٠ ٠	69.9		c	c	<u>~</u>	78	•	_	c
· ~	X 2 7 0 7	. 11	0 44	•	6 31	; _	; c	) c	7.	- 6	4 6	٠ (	• •
			•	•	10.0	•	•	9 (	0 (	7:	<b>V</b>	= 1	>
<b>-</b>	80178		0.24	·	0.39	ċ	<b>ɔ</b>	0	13	ж У	С	~	С
_	82709	u.	45.0	÷	6.87	•	C	c	_	91	2	c	C
-	82710	<b>L</b>	44.0	14.2	6.50	15.2	C	0	17	80	က	С	С
GROUP MEAN	MEAN		44.0	14.0	6.55	14.2			99				
2	82726	4	44.0	4	•	4	С	0	ß	92	7	c	ا <del>حد</del> م
~	82727	ц.	41.0	ω,	•	7.	С	С	9	94	c	c	C
~	82728		43.0	4		5	0	0	· œ	88	٠.	۰ د	· C
~	82729	ī	51.0	S	99.9	16.0	0	0	13	84		: ~	C
2	82730		40.0	•	6.36	15.6	С	0	6	06	-	c	0
GROUP	MEAN		43.8	13.9	6.30	17.8							
ĸ	82746	u.	47.0	4.	6.63	9.6	С	С	34	64	2	c	C
m	82747		46.0	4	6.94	-	0	0	11	88	0		С
m	82748	ц.	44.0	13.0	6.46	23.9	C	0	15	81	m	~	0
m	82749		46.0	4	6.98	5.	0	0	9%	72	2	C	0
m	82750		44.0	<b>÷</b>	6.68	7	0	0	28	99	<b>,</b>	2	0
GROUP MEAN	MEAN		46.0	14.1	6.74	15.5			114				
4	82766		32.0	ċ	5.08	5	0	С	56	44	C	c	C
4	82767		41.0	2	6.17	4.	С	0	23	7.1	4	^	C
4	82768		46.0	4	5.70	6	C	C	46	i S	c	. –	; <b>O</b>
4	82769	ட	43.0	3	6.26	3.	0	0	28	20	_		· C
4	82770		44.0	13.5	5.82	21.0	c	C	36	59	0	· ~	· C
GROUP MEAN	MEAN		41.8	12.6	5.81	19.0			192				

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 2

		n					1		DIFFE	RENTIAL			1111
GROUP	ANIMAL	: ن	HCT	HGB	RBC	-	META	BAND	SEG	LYMPH	MUNC	EOSIM	BASD
NUMBE	K NJMBEK	<b>×</b>	*	3	MILLS		<b>3</b> €	<b>3</b> <	ж	<b>&gt;</b> ÷	34	<b>3</b> .f	<b>≫</b>
5	82786	u.	39.0	12,7	5.23	2	C	C	o	86	^	ĸ	3.0 0 0 9 86 2 3 0
ī	82787	u	48.0	15,3	7.11	~		: <	, , ,	7 2	<b>,</b>	٦ (	<b>S</b> (
4					4 4		>	>	† V	2	<b>-</b> 4	5	=
n	82/88	L	C***	14.0	6.50	_	0	c	19	42	C	7	C
ς.	82789	u.	43.0	13.5	6.79	•	0	C	6	06	-	ı <b>c</b>	: <
5	82790	u_	49.0	13.7	7.56	_	0	C	ۍ ۰	06	1 (1)	; <b>-</b>	÷ c
											,	1	;
GROUP MEAN	MEAN		44.6	13.8	6.64	17.2							

TABLE MO. 2 - IMDIVIDUAL HENATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS INITIAL

S ANIMAL E PROTHAROMBIN SECONDS SECOND	COAGULATION MIN SEC	30	1 12	1 14	1 25	1 18	1 20	1 25	1 20	1 25	1 10	1 20	1 23	1 20	1 12	1 10	1 10	1 15	1 15	1 14	1 16	1 20	1 05	1 14
S ANIMAL E R NUMBER X 82696 M 82698 M 82699 M 82710 M 82711 M 82711 M 82713 M 82739 M 82739 M 82756 M 82759 M		m d	5	2	~	2.	%	~	~	2	2.	2.	ě	÷	~	<b>-</b>	÷.	5	•				•	~
	νшх	82696	85928	82699	82700	GROUP MEAN	82716	82717	82718	82719	82720	GROUP MEAN	82736	82737	82738	82739	82740	GKOUP MEAN	82756	82757	82758	82759	82760	GROUP MEAN

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ATION SEC	2	ŝ	15	15	17	11
COAGULATION Min sec		1	-	-	<b>-</b> -	-
PROTHROMBIN SECONDS	11.8	13.1	13,3	13.6		12.8
n uu ×	u.	<u>u</u>	<u>u</u>	u.	u_	•
AN I MAL NUMBER	82786	82787	82788	82789	82790	MEAN
GROUP NUMBER	rv	'n	ĸ	ı,	Ś	GROUP MEAN

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEFKS
WEEK 1

COAGULATION MIN SEC	1 11			0 57	0 54	1 03	1 08	0 54	1 03		0 52	1 01	0 46	0 56	0 58	1 01		95 0	1 00			0 47	1 05	95 0
PROTHROMBIN SECONDS	14.9	4	ŝ	15.1	ŝ	15.2	7	•	15.7	•	2	12.8	16.9	Š		12.4		13.5	14.4			14.5	2	13.7
S GROUP ANIMAL E MUMRER NUMBER X	1 82696 M	82697	85698	1 82699 M	82700	GROUP MEAN	82716	82717	2 82718 M	82719	82720	GROUP MEAN	82736	82737	82738	'n	82740	GROUP MEAN	82756	82757	82758	4 82759 M	82760	GROUP MEAN

The state of the s

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBING RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 1

ATION	10 56 01	57 57 59
COAGULATION MIN SEC	1010	°° •
PROTHROMBIN SECONDS	13.3 11.6 13.6	11.9 15.2 13.1
vш×	E E E	ΣΣ
AN IMAL NUMBER	82776 82777 82778	82779 82780 MEAN
GROUP NUMBER	יט אט יט	5 82 5 82 6ROUP MEAN

TABLE NO. 2 - IMDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING HR-2823 FOR TWO WEEKS
WEEK 2

12	08	54	15	18	60	21	0.8	9	15	53	11	57	16	90	11	0.7	0.7		10	17	0.1	23	03
-	1	C	-	~	<b>~</b> −1	-	_		_	С	7	С		<b>~</b>	-	-	-	C	~	-	-	С	7
•	4	4	ċ	0	12.1	•	•	•	•	•	12.4	•	•	14.6	14.4	•	12.8	•	•			•	12.8
96	25	86	66	00	MEAN	2716	2717	2718	2719	2720	MEAN	736	737	738	739	740	МЕАМ	756	757	158	759	160	MEAN
	-	ı	-	1	GROUP	2	2	2	2	~	GROUP	m	æ	m	ĸ	æ	GROUP	4	4	4	4	4	GROUP
	96 M 11.5 1 1	82696 M 11.5 1 1 82697 M 14.1 1 0	82696 M 11.5 1 1 82697 M 14.1 1 0 82698 M 14.1 0 5	82696 M 11.5 1 1 82697 M 14.1 1 0 82698 M 14.1 0 5 82699 H 10.3 1 1 1	6 M 11. 7 M 14. 8 M 14. 9 H 10.	82696 M 11.5 1 1 82697 M 14.1 1 0 82697 M 14.1 0 5 82699 M 10.3 1 1 1 82700 M 10.7 1 1 0 MEAN 12.1 1 0	82696 M 11.5 82697 M 14.1 82698 M 14.1 82699 H 10.3 82700 M 10.7 1 MEAN 12.1 1	82696 M 11.5 82697 M 14.1 82698 M 14.1 82699 H 10.3 82700 M 10.7 MEAN 12.1 1 82716 M 11.3	82696 M 11.5 82697 M 14.1 82698 M 14.1 82699 H 10.3 82700 M 10.7 MEAN 12.1 1 82716 M 11.3 82716 M 11.3	82696 M 11.5 82697 M 14.1 82698 M 14.1 82699 H 10.3 82700 M 10.7 MEAN 12.1 1 82716 M 11.3 82716 M 11.3 82718 M 12.1 82718 M 13.5	82696 M 11.5 82697 M 14.1 82698 M 14.1 82699 M 10.3 82700 M 10.7 NEAN 12.1 82716 M 11.3 82717 M 12.1 82717 M 12.1 82718 M 11.3 82718 M 13.5 1 1 0 82718 M 13.5	82696 M 11.5 82697 M 14.1 82699 M 10.3 82699 M 10.7 10.7 11.3 82716 M 11.3 82717 M 12.1 82718 M 13.5 82719 M 11.1 82720 M 13.5	82696 M 11.5 82697 M 14.1 82698 M 14.1 82699 M 10.3 82700 M 10.7 12.1 13.1 82716 M 11.3 82717 M 12.1 82718 M 13.5 82718 M 13.5 82720 M 13.5	82696 M 11.5 82697 M 14.1 82698 M 14.1 82699 M 10.3 82700 M 10.7 12.1 82716 M 11.3 82717 M 12.1 82718 M 13.5 82718 M 13.5 82720 M 13.5 MEAN 12.4 11.0	82696 M 11.5 82697 M 14.1 82698 M 14.1 82699 M 10.3 82700 M 10.7 12.1 13.1 82716 M 11.3 82717 M 12.1 82718 M 13.5 82718 M 13.5 82718 M 13.5 8273 M 11.0 82736 M 12.7	82696 M 11.5 82697 M 14.1 82698 M 14.1 82699 M 10.3 82700 M 10.7 12.1 82716 M 11.3 82717 M 12.1 82718 M 13.5 82719 M 11.1 82736 M 13.9 MEAN 12.7 82736 M 12.7 82736 M 12.7	82696 M 11.5 82697 M 14.1 82698 M 14.1 82699 H 10.3 82700 M 10.7 12.1 13.1 82716 M 11.3 82717 M 12.1 82716 M 11.3 82717 M 12.1 82718 M 12.1 82730 M 13.5 82730 M 11.0 11.0 82736 M 12.7 11.0 82736 M 12.7	#2696 M 11.5 #2697 M 14.1 #2697 M 14.1 #2699 H 10.3 #2700 M 10.7 1 #2717 M 12.1 1 #2717 M 12.1 1 #2718 M 11.3 #2720 M 13.5 #2720 M 13.9 0 #EAN 12.7 0 #2736 M 12.7 0 #2737 M 11.0 1 #2736 M 12.7 0 #2737 M 11.0 1	#2696 M 11.5 #2697 M 14.1 #2698 M 14.1 #2699 M 10.3 #2700 M 10.7 1 #2700 M 12.1 1 #2715 M 12.1 1 #2718 M 13.5 #2719 M 11.1 1 #2730 M 13.9 0 #6AN 12.7 0 #2736 M 12.4 1 #2736 M 12.4 1	R2696 M 11.5 R2697 M 14.1 R2698 M 14.1 R2699 M 10.3 R2699 M 10.7 R2700 M 11.3 R2716 M 11.3 R2717 M 12.1 R2716 M 11.3 R2718 M 13.5 R2719 M 11.0 R2736 M 12.4 R2736 M 12.4 R2736 M 12.4 R2736 M 12.4 R2736 M 12.4 R2736 M 12.4 R2737 M 11.0 R2737 M 11.0 R2737 M 11.0 R2737 M 12.4 R2738 M 14.6 R2737 M 11.0	R2696 M 11.5 R2697 M 14.1 R2698 M 14.1 R2699 M 10.3 R2699 M 10.7 R2700 M 11.3 R2716 M 11.3 R2717 M 12.1 R2716 M 11.3 R2718 M 13.5 R2719 M 11.0 R2736 M 12.4 R2736 M 12.4	R2696 M 11.5 R2697 M 14.1 R2699 M 10.3 R2699 M 10.7 R2699 M 10.7 R2700 M 11.3 R2716 M 11.3 R2717 M 12.1 R2718 M 13.5 R2719 M 11.1 R2719 M 11.0 R2730 M 12.4 R2730 M 12.4 R2750 M 12.4 R2750 M 12.4	#2696 M 11.5 #2697 M 14.1 #2698 M 14.1 #2699 H 10.3 #2700 M 10.7 1 #2717 M 12.1 1 #2718 M 12.1 1 #2719 M 11.1 #2719 M 11.0 0 #2730 M 12.4 1 #2734 M 12.4 1 #2735 M 12.4 1 #2736 M 12.4 1 #2739 M 14.6 #2739 M 14.6 #2739 M 14.6 #2739 M 14.6

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 2

193-404

ATION	SEC	04	19	58	0.1	12	10
COAGULATION	Z E	-	-	0	~	-	-
PROTHROMBIN	SECONDS	12.3	12.6	15.2	12.8	11.1	12.8
Sυ	×	Σ	I	Σ	Ξ	Σ	
ANIMAL	NUMBER	82776	82777	82778	82779	82780	MEAN
GROUP	NUMBER	'n	3	Z	5	, rv	GROUP MEAN

TABLE MO. 2 - IMDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS INITIAL

ATION SEC	0 0 m C 0	4	7 14 6 0 14	8 113 12 15	11 17 15 14 18 22
COAGULATION Min Sec		1			
PROTHKUMBIN SECONDS	11.2 12.8 10.9 11.2	11.9	10.2 11.0 12.6 12.5 11.9	11.6 10.5 10.6 12.9 14.2	12.1 11.4 10.6 13.5 12.1 11.5
νш×	птппп		or or or or	ппппп	шишиц .
AN IMAL NUMBEK	82706 82707 82708 82709 82710	MEAN	82726 82727 82728 82729 82730	MEAN 82746 82747 82748 82749	HEAN 82766 82768 82768 82770 HEAN
GROUP		GROUP	20000	GKOUP GROUP BBBBBBBBBBBBBBBBBBBBBBBBBBBBBBBBBBBB	GR OUP  4  4  4  4  6  GR OUP

- - oak

ble

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO MEEKS INITIAL

CDAGULATION Min Sec	10 05 16 11 09	10
COAGU! M IN	~ ~ ~ ~ ~	7
PROTHROMBIN SECONDS	14.0 13.8 12.6 12.0	13.2
Sm×	SEEEE	
ANIMAL NUMBER	82776 82777 82778 82778 82779	MEAN
GR OUP NUMBER	יט יט יט יט יט	GROUP MEAN

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEFK 1

ATION SEC	0.2	00	0.5	60	01	03	59	08	57	14	65	03	0.5	60	0.2	53	90	03	10	0.8	0.5	59	22	040
COAGULATION NIN SEC	-	_	. ~	_		~	0	~	С	-	0	1	-	~	-	0	-	1	-	-	· ~	0	0	-
PROTHROMBIN SECONDS	•	2	_	•	1.	11.8	11.4	13.8	-	12.5	•	12.3	13.4	8.6	•	3	15.1	12.4	12.3		•		~	12.5
S ANIMAL E NUMBER X	901	2707	2708	0	2710	MEAN	726	2727	2728	82729 F	2730	MEAN	146	747	748	82749 F		MEAN	991	2767	82768 F	691	2770	MEAN
GROUP NUMBER	-	-		1	-	GROUP	~	2	2	2	2	GROUP A	e	m	m	m	6	GROUP	4	4	<b>,</b> 4	4	4	GRUUP

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 1

	ATION	SEC	56	55	0.2	90	51	58
	COAGULATION	MIN	0	С	-	-	0	0
	PROTHROMBIN	SECONDS	11.7	12.0	14.3	10.8	12.9	12.3
S	نكا	×	щ	ц	ů.	u_	ட	
	ANIMAL	NUMBER	82786	82.787	82788	82789	82790	MEAN
	GROUP	NUMBER	2	5	5	z,	2	GROUP MEAN

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

		n				
GRUUP	ANINAL	u.	PROTHROMBIN	COAGULATION	ATION	
NUMBER	NUMBER	×	SECONDS	Z Z Z	SEC	
<del></del>	$\sim$	u_		-	15	
	~	ų.	8	-	60	
7	82708	u_	11.0	-	10	
7	2	u.	~	<b>,1</b>	0.7	
<b>-</b>	2	u_		1	0.1	
GROUP I	MEAN		12.3		υB	
2	272	u.	14.9	0	56	
2	272	u.		-	90	
2	82728	u.	12.7	-	12	
2	272	u.	9	-	04	
2	273	u_	•		10	
GROUP	MEAN		13.0		90	
m	$\sim$	u_	21.2	-	10	
т	~	ı	7	~	13	
m	82748	u.	18.9	-	0.5	
m	2	u,	Š		19	
6	82.750	u_	4.	1	0.1	
GROUP 1	MEAN		17.4	-	10	
4	82766	u_	•		23	
4	2	u_	-	~	17	
4	82768	<u>.</u>	2.	<b>,</b> 4	15	
4	$\sim$	ш	~	-	10	
4	$\sim$	щ		С	53	
GROUP	MEAN		13.8	-	12	

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 2

COAGULATION MIN SEC	1 04 1 00 1 15 1 07 0 59	1 05
PROTHROMBIN SECONDS	14.7 17.4 13.4 14.7 12.8	14.6
νшх	<b>44.4.4.4</b>	
AN IMAL NUMBER	82786 82787 82788 82789 82790	4EAN
GROUP NUMBER	พพณพพ	GROUP MEAN

TARLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
INITIAL

	ALK, PHOS	K-A.UNITS	64.0	42.8	46.0	46.8	76.6	55.2	80.8	0.99	130.+*	50.8	9.65	64.3	54.0	43.8	36.0	73.6	4.7.4	51.0	79.2	29.0	45.4	41.4	30.0	51.0
	SGPT	₹ 1 •	37.5	36.0	39.0	29.0	36.0	35.5	41.0	45.5	41.0	36.0	37.5	39.6	34.0	42.5	34.0	37.5	29.0	35.4	•				23.0	31.3
		M6%	16.0	12.0	16.0	17.0	17.0	15.6	20.0	16.0	15.0,	14.0	16.0	16.2	15.0	17.0	16.0	15.0	14.0	15.4	16.0	16.0	14.0	14.0	13.0	14.6
	GLUCOSE	WG%	50.0	40.0	39.0	68.0	51.0	46.6	73.0	45.0	44.0	0.09	0.89	58.0	0.99	73.0	81.0	77.0	0.99	72.6	78.0	91.0	81.0	82.0	73.0	81.0
n			Σ	Σ	Σ	Σ	Σ		Σ	I	Z	Σ	Σ		Σ	_	Σ	_	_		Σ	Σ	Σ	Σ	Σ	
	ANIMAL		82701	82702	82703	82704	82705	MEAN	$\sim$	~	72	72	72	MEAN	82741	82742	82743	82744	82745	MEAN	82761	82762	82763	82764	82765	MEAN
	GROUP	NUMBER	~	-	-	-	1	GROUP	2	7	7	7	2	GROUP	ĸ	m	m	ĸ	m	GROUP	4	4	4	4	4	GROUP

# = VALUE NOT INCLUDED IN MEAN

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES ALBIND RATS RECEIVING WR-2823 FOR TWO WEEKS INITIAL

	S		
	ALK.PHOS K-A.UNITS	41.4 44.8 71.0 53.4 53.4	52.8
	SGPT R-F.	31.0 34.0 28.0 36.0	32.6
1	BUN MG%	15.0 14.0 16.0 14.0	15.2
	GLUCOSE MG%	80.0 68.0 94.0 80.0	82.0 15.2
	νшх	ΣΣΣΣΣ	
	AN I MAL NUMBER	82781 82782 82783 82784	MEAN
	GROUP NUMBER	משמשמים	GROUP MEAN

TARLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES ALBINO RATS RECEIVING MR-2823 FOR TWO WEEKS WEEK 1

Ņ																								
ALK.PHUS K-A.UNITS	70.4	51.2	48.8	4.09	61.2	58.4	65.6	88.8	79.2	53.2	9.86	76.1	103.6	61.2	78.4	109.2	87	88.0	ന	2	82	4	34.4	7 20
SGPT R-F.	34.0	29.0	28.0	26.0	36.0	30.6	31.0	34.0	32.5	31.0	32.5	32.2	29.0	29.0	29.0	39.0	34.0	32.0	6	1	6	4	26.0	1 12
MG%	14.0	13.0	4	13.0	5	13.8	14.0	14.0	16.0	12.0	15.0	14.2	14.0	13.0	14.0	16.0	14.0	14.2	21.0	18.0	15.0	14.0	14.0	16.4
GLUCUSE MG%	63.0	0.49	0.69	59.0	0.49	63.8	0.99	74.0	0.69	55.0	89.0	70.6	84.0	103.0	86.0	0.46	75.0	88.4	100.0	108.0	100.0	103.0	87.0	9 66 .
νшх	Σ	I	Ŧ	I	T		Σ	Έ	Σ	Σ	I		Z	Ξ	Σ	Ξ	Σ		Ξ	Σ	Ξ	Ξ	Σ	
ANI HAL NUMBER	270	92702	270	270	2 70	MEAN	272	272	82723	272	72	MEAN	274	274	82743	274	274	MEAN	276	276	276	82764	276	X LAN
GROUP NUMBER	1	_	-	<b>,-</b> -	-	GROUP 1	~	7	7	~	7	GROUP A	m	m	m	m	m	GROUP	4	4	4	4	4	GROUP

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBIND RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 1

	ALK.PHUS	K-A-UNITS	40.8	40.0	87.6	62.0	50.4	56.2
	SGPT	R-F.	28.0	41.0	29.0	34.0	32.5	32.9
	RUR		17.0	14.0	16.0	15.0	14.0	15.2
	GLUCOSE	¥9×	78.0	71.0	83.0	76.0	72.0	76.0 15.2
S	ш	×			Σ			
	ANIMAL		82781	82782	82783	82784	82785	MEAN
	GROUP	NUMBER		ß	\$	ĸ	S	GROUP

TARLE NO. 3 - INDIVIDUAL RLOOD CHEDISTRY VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO HEEKS WEEK 2

	S	TS																								
	ALK.PHOS	K-A.UNI	36.8	27.6	36.0	44-0	38.8	36.6	49.6	46.0	45.6	30.0	35.2	41.3	50.4	27.2	30.8	2 · 44	39.6	45.6	8 70	7 02	56.0	37.6	36.0	59.0
	SGPT	× 1.	29.0	25.0	34.0	29.0	39.0	31.2	25.0	34.0	28.0	29.0	25.0	28.2	28.0	28.0	26.0	29.0	36.0	29.4	36.0	٠ (	31.0	1 3	37.5	34.2
7	HUN	<b>H</b> (2×	16.0	14.0	16.0	19.0	17.0	16.4	16.0	16.0	19,0	15.0	14.0	16.0	14.0	14.0	15.0	18.0	18.0	15.8	20.0	17.0	13.0	15.0	13.0	15.6
NEFK	GLUCUS E	M5.4	92.0	100.0	104.0	101.0	0.06	4.76	0.06	122.0	130.0	95.0	118.0	110.4	134.0	119.0	89.0	136.0	93.0	114.2	136.0	109.0	175.0	128.0	157.0	141.0
	S m s					Z	_		Σ	z	Σ	Z	Σ		Σ	Σ	Σ	Σ	Σ		Σ	Σ	Σ	I	Œ	
	ANIMAL	MONITOR	82701	82702	82703	82704	82705	MEAN	2	72	72	82724	72	MEAN	82741	82742	27	27	27	MEAN	32761	82762	82763	82764	82765	MEAN
	GROUP MUMR ED		-	_	7	-	-	GROUP A	2	2	7	7	7	GROUP M	М	m	m	m	m	GROUP M	4	4	4	4	4	GROUP M

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 2

	ALK.PHOS	K-A.UNITS	c	2000	28.8	α <b>α 7</b>	0.00	36.4	30.0	•	, 30	20.4
	SGPT	R-F.	000	0.62	26.0	34.0	•	31.0	32.5	•	200	20.00
	BUN	MG%	0	? • c	17.0	15.0		16.0	16.0	· •	7 71	† • o T
	GLUCOSE	₩ <b>0</b> %	103.0	0.001	0.66	98.0	•	76.0	82.0		01 6 16 7	017
S	ш		3	-	5	Σ		Σ	Σ			
	ANIMAL		82781	10.70	82782	82783		82784	82785		NATA	
	GROUP	NUMBER	ď	١	ī	'n	ı	'n	5		GROUP MEAN	

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES ALBIND RATS RECEIVING WR-2823 FOR THO WEEKS INITIAL

	ALK.PHUS	K-A.UNITS	26.0	30.2	22.0	24.8	32.8	27.2	50.0	0.49	28.0	0.99	0.94	8°05				38.2	31.0	30.4	46.8	23.0	38.6	22.4	31.6	32.5
	SGPT	ጽ ተ	28.0	26.0	32.5	34.0	31.0	30•3	39.0	36.0	36.0	39.0	36.0	37.2	34.0	39.0	37.5	31.0	31.0	34.5	34.0	_	37.5	25.0	28.0	31.1
	BUN	₩ ₩ ₩	18.0	16.0	18.0	16.0	18.0	17.2	17.6	•	19.0	21.0	18.0	18.2	19.0	21.0	19.0	20.0	19.0	9.61	5	2	23.0	œ	8	19.2
	GLUCUSE	MC%	0.49	0.69	61.0	0.09	72.0	65.3	61.0	72.0	74.0	81.0	0.96	76.8	46.0	0.89	55.0	51.0	62.0	56.4	52.0	0.09	72.0	71.0	75.0	0.99
S	ш:	×	ц.	u_	<u>.</u>	т	u_		u_	<u>u</u>	ц.	u.	u.		ı	u.	ı.	ı	u_		u_	u_	u.	u.	u_	
	ANIMAL		82711	71	7	7	71	MEAN	73	82732	73	33	73	MEAN	275	275	275	82754	275	MEAN	277	277	82773	277	277	MEAN
	GROUP	NUMBER	~		-	-	-	GROUP	2	2	7	2	2	GROUP	m	m	m	m	w	GROUP	4	4	4	\$	4	GROUP MEAN

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES ALBIND RATS RECEIVING WR-2823 FOR TWO WEEKS INITIAL

ALK.PHOS K-A.UNITS	33.2 51.8 27.4 30.6	40.0
SGPT R-F.	34.0 23.0 26.0 34.0	30.2
BUN MG%	18.0 23.0 18.0 19.0	19.4
GLUCUSE MG%	80.0 79.0 84.0 76.0	79.8 19.4
νш×	<b>unana</b>	
ANIMAL	82791 82792 82793 82794 82795	MEAN
GROUP NUMBER	មេសមម	GROUP

TARLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 1

ALK.PHUS K-A.UNITS	29.6 30.8 28.4 31.6	33.0 106.8 83.6 50.4	500	50.4 62.0 54.0 70.4 69.2	61.2 109.2 61.2 94.8 63.2 103.6
SGPT R-F.	26.0 22.0 28.0 37.0 31.0	28.2 25.0 36.0 26.0	29.0 31.0 29.4	34.0 39.0 31.0 39.0	36.1 34.0 31.0 34.0 37.5 34.0
BUN MG%	14.0 13.0 17.0 19.0	16.2 18.0 19.0	~ <del>&amp;</del> &	15.0 15.0 15.0 14.0	15.0 20.0 17.0 21.0 15.0 20.0
GLUCOSE NG%	69.0 67.0 80.0 80.0	74.2 105.0 90.0 74.0	91.0 89.0 89.8	121.0 89.0 105.0 95.0 78.0	97.6 93.0 112.0 157.0 131.0 102.0
хшх	шшшшш	<b>a a a</b>	<b>u</b> . u.	$\alpha$	$\alpha$ $\alpha$ $\alpha$ $\alpha$
ANI MAL NUMBER	82711 82712 82713 82714 82715	MEAN 82731 82733 82733	273 273 8	82751 82752 82753 82754 82755	MEAN 82771 82772 82773 82774 MEAN
GROUP NUMBER		GROUP 2 2 2	2 2 GROUP	пиппп	GROUP  4 4 4 4 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBIND RATS RECEIVING WR-2823 FOR TWO WEEKS

	ALK.PHOS K-A.UNITS	55.6 36.8 30.8 31.6	42.1
	SGPT R-F.	29.0 26.0 26.0 28.0 32.5	28.3
_	BUN MG%	16.0 18.0 15.0 19.0	17.0
WEEK 1	GLUCOSE NG%	78.0 97.0 80.0 86.0	87.4 17.0
	SШX	<u> </u>	
	ANI MAL NUMBER	82791 82792 82793 82794 82795	MEAN
	GROUP NUMBER	w w w w w	GROUP

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS
WEEK 2

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ALK.PHOS K-A.UNITS	19.6 20.0 14.4 16.8 30.0	20.2	30.8 27.6 21.6 30.8	30.8 23.6 26.8 24.0 28.8	25.9 34.4 29.6 56.0 49.6 48.4
SGPT K-F.	23.0 23.0 25.0 26.0	24.4		25.8 28.0 22.0 31.0	27.4 28.0 37.5 32.5 31.0 36.0
BUN MG%	16.0 17.0 16.0 16.0	16.8	14.0 19.0 15.0 18.0	17.2 17.0 15.0 18.0 16.0	17.8 16.0 17.0 15.0 16.0 16.0
GLUCUSE MG%	76.0 94.0 70.0 102.0	83.2	82 92 92 12 60	121.4 118.0 92.0 124.0 130.0	114.0 138.0 166.0 138.0 202.0 116.0
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ANI MAL MUMBER	82711 82712 82713 82714 82715	N 27	82732 82733 82734 82735	MEAN 82751 82752 82753 82754 82755	MEAN 82771 82772 82773 82774 82775
GROUP NUMBER		Δ.	12020	6R0UP 3 3 3 3	6R0UP 4 4 4 4 6 6R0UP

TARLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 2

ALK.PHOS K-A.UNITS	31.2 19.6 36.0 12.8 23.6	24.6
SGPT R-F.	25.0 23.0 23.0 20.0 22.0	22.6
BUN MG%	16.0 16.0 16.0 20.0 16.0	16.8
GLUCOSE MG%	90.0 114.0 110.0 100.0 159.0	114.6 16.8
×πν	<b></b>	
ANIMAL NUMBER	82791 82792 82793 82794 82795	MEAN
GROUP NUMBER	ר הו הי הי הי	GROUP

TABLE NO. 4 - URINE ANALYSIS ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS INITIAL

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RACT	MANY	MANY	MANY	MANY	MANY
DINGS	FEW		FER		
BC WBC EPITH AMORPH CRYS BACT SPERM O-1		0-2	T.	LITTLE	
WBC WBC	1-0				1-3
x					
OCC BLD	O	C	0	o	c
SU- PRO- BILI- OCC GAR TEIN RUBIN BLD	0	0	0	О	С
PRO- Tein	C	C	С	0	0
SU- GAR	0	0	0	C	С
P H SP.GR.	7 1.015 0	7 1.015	7 1.009	7 1.021 0	7 1.011
	7	<b>~</b> ,	7	7	~
APPEAR.	T YEL	C YEL	C YEL	C YEL	C YEL
NUMBER S UF AN- E IMALS X	5 * X	χ. Σ	5* *	स	5# M
GROUP NUMBER	7	۸	ж	4	5

# = POOLED SAMPLES

TABLE NO. 4 - URINE ANALYSIS ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 1

	ĮΣ		→	-	_	
	SPEF		FF	FEW	FFW	
	S	MANY	MANY	MANY MANY	HANY MANY	HANY
	ND1NG CRYS	FEW	HANY	HANY	HANY	FEN
	MICROSCOPIC FINDINGSBC WBC EPITH AMORPH CRYS BACT SPERM	1-3 LITTLE FEW	LITTLE HANY HANY	МОСН	2-4 NUCH	0 0-1 1-2 1-3 LITTLE FEW
	ICROSC( EP I TH	1-3	0-1			1-3
	WBC	1-2	0-1	1-3	1-3	1-2
	×			0 0-1		0-1
	OCC BLD	0	0	c	0	C
4	PRO- BILI- OCC TEIN RUBIN BLD	С	<b>°</b> .	c	c	0, 0
	PRO- Tein	C	0	0	O	
	SU- GAR	0	0	0	c	0
	Р Н SP.GR.	7 1.012	7 1.013 0	7 1.012 0	7 1.005	7 1.012 0
	₫ I	7	7	7	-	7
	APPEAR.	T YEL	T YEL	T YEL	T YEL	T YEL
	NШX	Σ	Σ	Σ	Œ	Z
1	NUMBER OF AN- IMALS	\$	<b>₹</b>	rU #	\$	₹.
	GR <i>OUP</i> NUMBER	1	~	m	4	æ

\* = POOLEN SAMPLES

TABLE NO. 4 - URINE ANALYSIS ALBINU RATS RECEIVING WR-2823 FOR TWO WEFKS WEEK 2

SPERM	HANY	FEW			
BACT	MANY	FANY MANY	MANY	MANY	MANY
ND I NGS CRYS	MANY	FANY	MANY MANY	MANY MANY	MANY MANY
CROSCOPIC FINDINGSEPITH AMORPH CRYS BACT SPERM	LITTLE MANY MANY	мисн	мпсн	мисн	МОСН
MICROSCOPIC FINDINGSBBC WRC EPITH AMORPH CRYS BACT SPERM			8-10 MUCH	2-4	1-3
WBC	0-1	0-1	1-3	0-1	
RBC	1-2	0-1		1-3	2-4
918 000	0	o	c	0	<b>-</b>
BILI- RUBIN	C	0	0	C	C
PRO- TEIN	<b>-</b>	<b>-</b>	<b>├</b> ~	<b>-</b>	0
SU- GAR	0	C	0	С	С
P SU- PKO- BILI- OCC H SP.GR. GAR TEIN RUHIN BLD	1.026 0	1.024 0	1.017	1.022 0	1,018
σI	•	7	7	9	7
APPEAR.	T YEL	T YEL	T YEL	T YEL	T YEL
νшх	Σ	Σ	Σ	Σ	Z
NUMBER S GROUP OF AN-E NUMBER IHALS X	\$. *	¥ 50	¥ ₩	₹ \$	5. M
GROUP NUMBER		~	m	4	κ

\* = POOLEU SAMPLES

TABLE NO. 4 - URINE ANALYSIS ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS INITIAL

SPERM					
S BACT	MANY MANY	MANY	MANY	MANY	MANY MANY
NDI NGS CR YS	MANY		FEW	FEW	MANY
MICROSCOPIC FINDINGSBC WBC EPITH AMORPH CRYS BACT SPERM	МОСН				
W BC			1-2	4-5	2-3
RBC		2-3			
078 000	0	c	С	C	C
BILI- RUBIN	c	С	С	c	0
PRO- TEIN	o	0	0	0	0
SU- GAR	0	0	0	0	0
P SP.GR. GAR TEIN RUBIN BLD	7 1.023 0	7 1.020	7 1.016 0	7 1.021	7 1.010 0
a I	-	7	7	_	7
APPEAK.	T YEL	5* F C YEL	T YEL	C YEL	C YEL
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NUMBER S GROUP OF AN-E NUMBER IMALS X	₹. ਜ	ις. \$	₹. 1	አ ጥ	ις. *
GROUP	1	~:	w	4	72

\* = POOLED SAMPLES

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TABLE NO. 4 - URINE ANALYSIS ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 1

193-404

SPERM					
BACT	MANY	MANY MANY	MANY MANY	MANY MANY	MANY
NDI NGS CRYS	MANY MANY	MANY	MANY	MANY	FEW
MICROSCOPIC FINDINGS	мпсн	1-3 мосн	мисн	мпсн	LITTLE FEW
ICROSCI EPITH	1-3 1-2 MUCH	1-3			
¥BC	1-3		2-4	1-2	
RHC			0 1-3 2-4		
00CC 8LD	0	0	0	0	o
BILI- RUBIN	0	С	C	0	С
PRO- Tein	0	c	С	0	0
SU- GAR	0	0	C	C	0
P H SP.GR. GAR TEIN RUBIN BLD	7 1.022	1.018 0	7 1.013 0	7 1.010 0	7 1,008 0
σI	7	7	7	7	7
APPEAR.	T YEL	T YEL	T YEL	T YEL	T YEL
νшх	u.	% ∓	5. F	<u>u</u> .	5 F
NUMBER UF AN- IMALS	φ. *	₹C ¥	ŗ.	<b>₩</b>	5.
GROUP NUMBER	-	~	M	4	ĸ

\* = PUOLEN SAMPLES

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TABLE NO. 4 - URINE ANALYSIS ALBINO RATS RECEIVING WR-2823 FOR TWO WEEKS WEEK 2

193-40

SPERM					
S BACT	MANY MANY	MANY	MANY	MANY MANY	MANY
NDING!	MANY	LITTLE FEW	LITTLE MANY MANY	MANY	FEW
MICROSCOPIC FINDINGSBEC WBC EPITH AMORPH CRYS BACT SPERM	MUCH	LITTLE	LITTLE	MUCH	1-3 мисн
ICROSCO EP I TH				5-4	
MBC WBC	1-3	0-1	2-4	1-3	0-1
RBC	0-1	1-3			0 0-1
OCC BLD	c	<b>-</b>	0	C	С
SU- PRO- BILI- OCC GAR TEIN RUBIN BLD	С	c	0	C.	0
PRO- TEIN	С	0	0	0	С
SU- GAR	0	0	0	C	c
P H SP.GR.	7 1.013	7 1.020	6 1.020	6 1.017	6 1.018 0
₫ I	7	_	9	Ç	æ
APPEAR.	T YEL	T YEL	T YEL	T YEL	T YEL
SШX	ட	u.	uL.	Т	ட
NUMBER S GROUP OF AN- E NUMBER IMALS X	₹. T	Ŗ \$	₩. T	ţ.	5# F
GROUP	-	8	m	4	\$

\* = POOLED SAMPLES

#### HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: February 24, 1970

Material: WR-2823 (AU 69115)

Subject: REPORT NO. 30

Intravenous Toxicity Study - Dogs

Project No. 193-405

#### SUMMARY

WR-2823 (AU 69115) was administered intravenously at dosage levels of 50, 100, 200, and 400 mg/kg of body weight to four groups of two or four male dogs each for a total of one, four, or five doses.

Depression was noted in dogs receiving 50 and 100 mg/kg following the initial injection, and slight eye and nasal discharge was noted in the 50 mg/kg dogs during Week 1. One 100 mg/kg dog also exhibited loss of motor control, lethargy, and nasal discharge following the fourth injection. Signs noted in two 200 mg/kg dogs prior to death after the fourth or fifth injection included emesis, slightly elevated body temperature, dilated pupils, retching without emesis, depression, eye and nasal discharge (one dog), comatose appearance (one dog), and lack of motor control (one dog). The two additional 200 mg/kg dogs which received only one injection exhibited emesis of food mass, drooping eyelids, and listlessness or lack of energy with complete recovery within several hours after injection.

Emesis (one dog), inability to stand, dilated pupils, lack of pain reflex, and irregular respiration (one dog) preceded death in the 400 mg/kg dogs on the day of the initial injection. Body weight loss was noted in one Group No. 1 dog, in two Group No. 2 dogs, and in three Group No. 3 dogs.

The one compound-related alteration noted at necropsy was marked reddening of the renal cortex and/or medulla at the two higher levels.

#### MATERIAL

Identification WR-2823 (AU 69115).

Description Fine, white powder with no noticeable odor.

Receipt Date July 2, 1969.

Purity Assumed to be 100% active ingredient.

### METHODS

### Experimental Animals

Breed: Young adult purebred beagles.

Number: Ten males.

Body Weight (At Initiation): 7.2 to 12.8 kg.

Housing: Individually in metal cages.

Diet: Ground Wayne Dog Meal and water ad libitum.

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# Groups and Dosage Levels

Group No.	No. of Animals	Dosage Level each day	No. of Days Dose was Received
1	2	50 mg/kg	4
2	2	100 mg/kg	4
3	2 2	200 mg/kg 200 mg/kg	5 1
4	2	400 mg/kg	1

# Compound Administration

The test material was administered by intravenous injection as a 50% solution in distilled water according to the regimen outlined in the above table. Rate of administration was approximately 1 ml. per 10 seconds.

# Observations and Records

Daily: Appearance, behavior, and signs of compound effect.

Initially and Terminally: Body weights.

### Terminal Studies

Terminal Sacrifice: By exsanguination under anesthesia (Surital) generally nine days following the last intravenous injection.

Gross Necropsies: On all dogs which died during the study and on all dogs sacrificed at termination.

#### RESULTS

# Appearance, Behavior, Body Weight Changes, and Signs of Compound Effect

Group No. 1 (50 mg/kg): Slight depression following the second injection and slight clear-colored eye and nasal discharge during Week 1 were noted in both dogs. One dog showed a weight loss of 1.4 kg. (13%).

Group No. 2 (100 mg/kg): Both animals appeared slightly depressed following the second injection of compound and both animals exhibited terminal body weight loss (0.7 kg. or 8% and 0.8 kg. or 7%). In addition to these signs, loss of motor control, depression, lethargy, and nasal discharge were noted in one animal following the final injection.

### Group No. 3 (200 mg/kg):

Four or Five Injections - Following the initial injection, animals showed emesis of food mass or white, mucoid material; slightly elevated body temperature; dilated pupils; lethargy; and retching without emesis. Depression was noted after the third injection.

One animal died following the fourth injection, and one animal exhibited weakness and inability to stand.

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							_#	

Following the fifth injection, one animal showed eye and nasal discharge, comatose appearance, and lack of motor control with death occurring on the day after the fifth injection. Weight losses of 0.5 kg. (4%) and 0.3 kg. (3%) were noted.

One Injection - Emesis of food mass (one dog), drooping eyelids, and listlessness or lack of energy were noted following injection with signs subsiding within several hours following injection.

One animal exhibited a terminal body weight loss of 0.1 kg. (1%).

Group No. 4 (400 mg/kg): Emesis of food mass (one dog), inability to stand, dilated pupils, lack of pain reflex, and irregular respiration (one dog) were noted after injection with death occurring in both dogs on the day of injection.

### Gross Pathology

At Death: Large amount of blood on cut surface of spleen and liver (two 200 mg/kg level dogs and two 400 mg/kg level dogs); bile in gallbladder dark and thickened (one 200 mg/kg level dog); kidneys reddened and/or enlarged (one 200 mg/kg level dog and in one 400 mg/kg level dog); cortex and/or medulla of kidneys markedly reddened (one 200 mg/kg level dog and two 400 mg/kg level dogs); mucosal surface of urinary bladder reddened and contained calculi closely adhered to surface (one 400 mg/kg level dog); and skin around injection site purplish in color (one 200 mg/kg level dog).

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At Sacrifice: Spleen approximately twice normal size in one 100 mg/kg level dog.

Submitted by MARCELINA B. POWERS, D.V.M., M.S.

Project Manager, Drugs and

Industrial Chemicals

Toxicology-Biosciences Laboratory

Report Preparation: Lambert

Supervision: Pate

gmb

#### HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: January 14, 1970

Material: WR-2823 (AU 69115)

Subject: REPORT NO. 29

14-Day Subacute Intravenous Toxicity - Dogs

Project No. 193-406

#### SUMMARY

WR-2823 (AU 69115) was administered by intravenous injection as a 22.4% or 44.8% weight-per-volume solution in saline to four groups of two male and two female beagles each once daily for a total of 14 days at dosage levels of 20, 40, 80, and 160 mg/kg of body weight. One group of two male and two female beagles served as a control and received only saline.

All control animals were normal in appearance and behavior throughout the study, but all exhibited 8% to 12% body weight losses. Toxic signs noted in all test animals included slow or no pupillary response to light and/or relaxed nictitating membranes following early injections and within 10 to 30 minutes following each subsequent injection. Terminal body weight losses were noted in all test groups and ranged from 11% to 16% in Group No. 2 animals, from 10% to 25% in Group No. 3 animals, from 16% to 35% in Group No. 4 animals, and from 8% to 12% in Group No. 5 animals. Additional toxic signs noted in Group No. 4 animals included droopy eyes (two dogs) and excessive thirst (one dog) following the initial injection; sporadic episodes of emesis throughout the study; decreased activity during Week 2; mucoid

discharge from both eyes during Week 2 (Dog No. 14494); and slight nasal discharge and slight salivation during Week 2 (one dog). Additional toxic signs noted in Group No. 5 animals prior to total mortality by the latter part of Week 1 included emesis (one dog); inability to strid (one dog); listlessness and inactivity or decreased activity (two dogs); slight response to touch and no response to sound (one dog).

Clinical laboratory studies indicated a decrease in leukocyte count of Group No. 4 (80 mg/kg/day) animals at one and two weeks, a slight increase in the erythrocyte count in one or two animals at 80 mg/kg/day at two weeks, a slight increase in blood urea nitrogen values in treated males and females at one and two weeks, and an increase in blood sugar values in females at two weeks. Most of the values generally remained within the normal limits of variation; however, with some individual treated animals showing marked deviations from normal values. Urine analyses revealed no compound effects.

Gross necropsy findings revealed a compound-related enlargement of the spleen in all Group No. 5 animals. One Group No. 5 male and both Group No. 5 females showed high spleen weights and spleen/body weight ratios at termination.

Terminal ophthalmologic examination showed severe bilateral conjunctivitis with mucopurulent discharge and scleral injection in one Group No. 4 male (Dog No. 14494) and one Group No. 4 female (Dog No. 14458).

Dog No. 14458 also exhibited relaxed nictitating membranes. The cornea of these eyes were grossly normal, and eye transparency was not affected. These conditions were symptoms of compound-related systemic disease. No microscopic examination of the preserved tissues was performed.

#### MATERIAL

Identification WR-2823 (AU 69115).

<u>Description</u> Fine, white powder with no noticeable odor.

Receipt Date July 2, 1969.

Purity Assumed to be 100% active ingredient.

#### METHODS

# Experimental Animals

Breed: Young adult purebred beagles.

Number: Ten males and 10 females.

Body Weight: At initiation, 6.4 to 13.8 kg.

Housing: Individually in metal cages.

Diet: Ground Wayne Dog Meal and water ad libitum.

# Animal Groups and Dosage Levels

Group No.	No. of Animals male female	Dose Levels
1	2 2	control
2	2 2	20 mg/kg
3	2 2	40 mg/kg
4	2 2	80 mg/kg
5	2 2	160 mg/kg

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## Compound Preparation and Administration

The test material was administered by intravenous injection as a 22.4% weight-per-volume solution in saline to Groups No. 2 and No. 3 and as a 44.8% weight-per-volume solution in saline to Groups No. 4 and No. 5.

Group No. 1, control, received intravenous injections of physiological saline at the rate of 0.4 ml/kg of body weight. Doses were administered once daily for a total of 14 days.

# Observations and Records

Mortality and Pharmacotoxic Effects: Daily.

Body Weight: Initially, Day 5, Day 7, Day 8, Day 12, and terminally.

Ophthalmologic Examination: Initially and terminally.

### Clinical Laboratory Studies

Performed: Initially, at seven days, and terminally (14 days).

Hematological Studies: Hematocrit and hemoglobin determinations, erythrocyte count, total and differential leukocyte count, prothrombin time, and clotting time.

Blood Chemistry Studies: Determinations of blood urea nitrogen, fasting blood sugar, serum glutamic-pyruvic transaminase, and alkaline phosphatase.

Urine Analyses: Volume, pH, specific gravity, protein, glucose, bilirubin, occult blood, and microscopic examination of sediment.

Ophthalmologic Examination Performed initially and terminally.

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## Terminal Studies

- Terminal Sacrifice: By exsanguination under anesthesia (Surital) after 14 days of intravenous administration of the compound.
- Gross Necropsies: Performed on all animals which died during the study or were sacrificed at termination.
- Organ Weights: Weights for thyroid, heart, liver, spleen, kidneys, adrenals, and testes or ovaries were recorded for all animals at necropsy.
- Tissues Preserved: Brain, pituitary, thoracic spinal cord, thyroid, lung, heart, liver, gallbladder, spleen, kidney, adrenal, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testes, ovaries, prostate, uterus, rib junction, bone marrow, and nerve with muscle were preserved in 10% neutral buffered formalin. Eyes were preserved in alcoholic formalin.

#### RESULTS

- Appearance, Behavior, Body Weight Changes, and Signs of Compound Effect

  Individual body weights and compound administration are presented in
  Table No. 1.
  - Group No. 1 (Control 0.4 ml. Saline Per Kilogram of Body Weight): All animals in this group were normal in appearance and behavior throughout the study. Body weight losses of 1.5 kg. (12%), 1.3 kg. (10%), 1.2 kg. (10%), and 0.6 kg. (8%) were noted.

- Group No. 2 (20 mg. WR-2823 Per Kilogram of Body Weight): Slow pupillary reflex or relaxed nictitating membrane were noted following the fourth or fifth injection and within 10 to 30 minutes following each injection thereafter. Body weight losses of 1.3 kg. (13%), 1.2 kg. (11%), 1.4 kg. (16%), and 1.3 kg. (15%) were noted.
- Group No. 3 (40 mg. WR-2823 Per Kilogram of Body Weight): Slow pupillary response to light or no pupillary response to light (one dog) and/or relaxed nictitating membranes were noted following the third injection of compound and within 10 to 30 minutes following each subsequent injection. Body weight losses of 1.0 kg. (10%), 2.5 kg. (19%), 1.4 kg. (15%), and 1.6 kg. (25%) were noted.
- Group No. 4 (80 mg. WR-2823 Per Kilogram of Body Weight): Emesis of white mucoid material in two dogs and droopy eyes in two dogs were noted after the first injection. One animal also appeared to be very thirsty. Slow pupillary response to light and/or relaxed nictitating membranes were noted in all animals following the second injection and generally within five to 30 minutes following each subsequent injection.

  Decreased activity was noted in all animals during the second week of the study, and all animals exhibited sporadic episodes of emesis throughout the study. One animal showed mucoid discharge from both eyes during the early part of Week 2, and slight nasal discharge and slight salivation were noted in one animal during the early part of Week 2. Weight losses of 4.2 kg. (35%), 2.3 kg. (16%), 2.4 kg. (29%), and 2.2 kg. (21%) were noted.

Group No. 5 (160 mg. WR-2823 Per Kilogram of Body Weight): All animals exhibited emesis following the initial injection. One dog exhibited relaxed nictitating membranes and/or no pupillary response to light following the second and third injections. Following the fourth injection, this animal stood with head hanging and exhibited emesis twice with death occurring on the day after this injection. One dog exhibited relaxed nictitating membranes and no pupillary response to light following the second and third injections with death occurring within 45 minutes after the third injection. And ther dog showed no pupillary response to light, inability to stand, listlessness and inactivity, slight response to touch, and no response to light following the second injection with death occurring one hour after the third injection. The fourth animal exhibited no pupillary response to light following the second injection. Decreased activity, relaxed nictitating membranes, and no pupillary response to light were noted 10 minutes following the third injection with death 30 minutes postdose. Dogs showed terminal weight losses of 0.9 kg. (8%), 1.1 kg. (12%), and 1.2 kg. (12%). One terminal weight was inadvertently omitted.

### Clinical Laboratory Studies

Results of clinical laboratory studies are presented in Tables No. 2 (hematology), No. 3 (blood chemistry), and No. 4 (urine analyses).

All hematological values were generally within normal limits of variation. However, the leukocyte counts among the Group No. 4 animals tended to be somewhat lower at one and two weeks when compared both with control animals and with pretreatment values for those animals. In addition, slightly elevated erythrocyte counts were recorded for one male and one female dog in Group No. 4 at one week and in one Group No. 4 male at two weeks.

A review of blood chemistry data revealed two dose-related changes. Blood urea nitrogen values showed a slight dose-related increase in treated males and females at one and two weeks when compared with values for control animals. However, values generally remained within the normal limits of variation with the exception of one Group No. 4 male (Dog No. 14494) at one and two weeks and one Group No. 4 female (Dog No. 14458) at two weeks, both of which had higher than normal values. A dose-related increase in blood sugar values was noted in females at two weeks with one Group No. 3 female (Dog No. 14435) and two Group No. 4 females (Dogs No. 14458 and No. 14468) exhibiting values higher than the normal limits of variation. Group No. 4 males also exhibited high blood sugar values at two weeks.

Results of urine analyses showed no compound-related effects.

#### Ophthalmologic Examination

Initial and terminal eye examinations were performed using Mydriacyl as a mydriatic, a binocular indirect ophthalmoscope, and for some animals a direct ophthalmoscope. The following ocular changes were observed at the initial examination: slightly injected sclera in the left eye of Dog No. 14125 (Group No. 1 male); entropion of the left eye of Dog No. 14333 (Group No. 1 male); bilateral,

slight, veil-shaped cloudiness in vitreous of Dog No. 14355 (Group No. 2 female); and epiphora of the left eye of Dog No. 14417 (Group No. 3 female). The conditions present in Dogs No. 14333 and No. 14355 at initiation were still present at termination, and Dog No. 14468 (Group No. 4 female) had moderately injected sclera at termination. In addition, compound-related symptoms of systemic illness the form of severe bilateral conjunctivitis with mucopurulent discharge and scleral injection were noted in female Dog No. 14458 and male Dog No. 1449/ both of Group No. 4. Female Dog No. 14458 also showed relaxed nictitating membranes. The cornea of these eyes were grossly normal, and eye transparency was not affected.

## Gross Pathology

## At Death:

Group No. 5 - Liver pale in appearance in one female (Dog No. 14470); spleen enlarged in all animals; liver and thyroid enlarged in one male (Dog No. 14504).

At Sacrifice: Right thyroid 2 mm. by 3 mm. in size with cyst-like formation on anterior end in one Group No. 4 male (Dog No. 14494); small cyst at base of pituitary in one Group No. 2 female (Dog No. 14355); gallbladder not observable in one Group No. 2 female (Dog No. 14457); gallbladder distended in one Group No. 3 male (Dog No. 14389), one Group No. 3 female (Dog No. 14435), one Group No. 4 male (Dog No. 14502), and one Group No. 4 female (Dog No. 14458); one hookworm in small intestine of one Group No. 2 male (Dog No. 14251);

capsular surface of kidneys covered with gray, pitted areas in one Group No. 4 male (Dog No. 14494); capsular surface of kidneys rough with gray discoloration and medulla reddened in one Group No. 4 female (Dog No. 14458); capsular surface of kidneys white and pitted with medulla and hilus reddened in one Group No. 4 male (Dog No. 14502); capsular surface of kidney roughened and medulla reddened in one Group No. 3 male (Dog No. 14389); odd brown tinge to testes in one Group No. 4 male (Dog No. 14502); walls of urinary bladder thickened and/or mucosa reddened or hemorrhagic in appearance in one Group No. 1 female (Dog No. 14333), in one Group No. 2 male (Dog No. 14251), in two Group No. 2 females (Dogs No. 14355 and No. 14457), in one Group No. 3 male (Dog No. 14389), and in two Group No. 2 males (Dogs No. 14494 and No. 14502).

Organ Weights Individual terminal body weights, organ weights, and organ/body weight ratios are presented in Table No. 5.

One Group No. 5 male (Dog No. 14515) and both Group No. 5 females (Dogs No. 14470 and 14471) exhibited high spleen and spleen/body weight ratios. High kidney weights and kidney/body weight ratios were noted in one Group No. 5 male (Dog No. 14515) and one Group No. 5 female (Dog No. 14471). Low liver weights and liver/body weight ratios were noted in one Group No. 2 female (Dog No. 14355), in one Group No. 3 female (Dog No. 14435), and in two Group No. 4 females (Dogs No. 14458 and No. 14468). High liver weights and liver/body weight ratios were observed in one Group No. 1 female (Dog No. 14348) and in two Group No. 5 females (Dogs No. 14470 and No. 14471).

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Histopathological Evaluation No microscopic examination of tissues was performed; however, all preserved tissues are being stored at Hazleton Laboratories, Inc., for possible future reference.

Submitted by MARCELINA B. POWERS, D.V.M., M.S.

Project Manager, Drugs and

Industrial Chemicals

Toxicology-Biosciences Laboratory

Report Preparation: Lambert

Supervision: Pate

gbb

## EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

- T = trace (±)
- 0 = negative
- 1 = slight (+)
- 2 = moderate (++)
- 3 = marked (+++)
- 4 = severe (++++)

TNTC = too numerous to count

Table No. 1 - Individual body weights and compound administered for male and female purebred beagles.

		CROUP	NO. 1 - CO	NTROL (0.4 M	L. SALINE	GROUP NO. 1 - CONTROL (0.4 ML. SALINE PER KG. BODY WEIGHT)	WEIGHT)	
	2000	0. 14121	DOG NO	DOG NO. 14125	N DOG	DOG NO. 14333	DOC 1900	DOC NO. 14348
INTERVAL	F.	WT. COMPOUND	WT.	COMPOUND	<u>.</u>	COMPOUND	VI.	ml.
	K8.	nl.	kg.	mJ.	× 00	•	•	Ì
	,		0 61		11.2		7.0	
	11.9		13.0	6	1	4		2.8
		8.4		7.6		) v		2.8
2		4.8		5.2		4. U.		, «
ım		4.8		5.2		 		2.8
4		4.8		2.5	•		6.7	2.7
· •ኅ	11.3	4.5	12.5	5.0	10.6	4.2		7-7
· •		4.5		2.0	4	7.6	-	. α ι ς
, ~	11.3	4.5	12.2	6.4	10.3	7.4	1:,	9 4
- 0	a ct	7.7	11.8	4.7	10.0	0.4	6.0	0.7
<b>o</b> «		, ~		4.7		4.0		7.0
s.		. ·				0.4		5.6
01		4. V.		· ·		0.4		2.6
I		4.3			10	4.7	9.9	5.6
77	11.0	4.4	12.3	y .	70.7	. 4	1	2.6
13		7.7	10.5	7.4	•		9	2.4
14	10.5	4.2	11.7	4.7		5.7	9 9	i
Terminal	10.4		11.7		9.6		; 5	
Wt. Change, kg.	-1.5		-1.3		-1.2		9.0	
					-			

Table No. 1 - Continued

#TWB	2	ł	ROUP NO. 2	GROUP NO. 2 - 20 MG. WR-2823 PER KG. OF BODY WEIGHT	823 PER KG	OF BODY WE	- 1	
THE	3	W. 14231	3	DOG NO. 14253	DOC .	DOC NO. 14355	DOG NO. 14457	14457
INTERVAL	E	COMPOUND	M	COMPOUND	5	COMPOUND	WT.	COMPOUND
days	ж Э	.88	ж Э	• 8 <del>1</del>	k8.	· Su	K8.	196.
Initial	7.6	ital 9.7	10.5		8.4		9.8	
1	•	0.97		1.1		0.84		0.86
, ,		0.97		1.1		0.84		98.0
m •		0.97		1.1		0.84		0.86
<b>4</b>		0.97		1.1		0.84		98.0
۰ م	10.0	1.0	10.4	1.0	7.7	0.77	8.8	0.88
9		1.0		1.0		0.77		0.88
_	9.	96.0	9.7	0.97	8.0	0.80	8.4	0.84
<b>••</b> •	9.1	0.91	9.3	0.93	7.3	0.73	8.2	0.82
ر م		0.91		0.93		0.73		0.82
01		0.91		0.93		0.73		0.82
11		0.91		0.93		0.73		0.82
12	9.0	0.0	9.5	0.95	7.7	0.77	8.5	0.85
13		0.0		0.95		0.77		0.85
14	8.1	0.81	9.5	0.92	7.1	0.71	7.9	0.79
Terminal	8.4		9.3		7.0		7.3	) •
Wt. Change, kg.	-1.3		-1.2		-1.4		-1.3	

Table No. 1 - Continued

į.		- 1	ROUP NO. 3	GROUP NO. 3 - 40 MG. WR-2823 PER KG. OF BODY WRIGHT	823 PER KG	OF BODY WEI	GHT	
THE	200	NO. 14366	200	DOG NO. 14389	DOC	DOG NO. 14417	DOC M	DOG NO. 14435
INTERVAL	M	COMPOUND	M.	COMPOUND	WT.	COMPOUND	.TA	COMPOUND
days	kg.	kg. mg.	k8.	.88	kg.	. 8m	k8.	.98
Initial	9.6		12.7		9.0		4.4	
-		1.9		2.5	) •	8.1	;	-
7		1.9		2.5				. E.
m ·		1.9		2.5		1.8		1.3
4		1.9		2.5		1.8		1.3
<b>.</b>	9.6	1.9	12.0	2.4	8.3	1.7	5.7	7,1
•		1.9		2.4		1.7	•	-
7	9.0	1.8	11.3	2.3	8.4	1.7	2.6	1 -
<b>∞</b>	8 .5	1.7	10.8	2.2	8.0	1.6	4.0	1:1
σ.		1.7		2.2		1.6	•	
10		1.7		2.2		1.6		: - -
11		1.7		2.2		9.7		: -
12	9.5	1.8	10.5	2.1	8.1	1.6	*	1.6*
13		1.8		2.1		1.6	5.0	1.0
14		1.7	10.0	2.0	7.5	1.5	8.4	)   
Terminal			10.2		7.6	)	4.8	
Wt. Change, kg.	-1.0		-2.5		-1.4		-1.6	

\* Technical error in weighing; animal received incorrect dose.

Table No. 1 - Continued

			ROUP NO. 4	GROUP NO. 4 - 80 MG. WR-2823 PER KG. OF BODY WEIGHT	2823 PER KG	. OF BODY WE]	GHT	
TIME	DOC 5	16	N 900 I	DOG NO. 14502	200 E	DOG NO. 14458		DOG NO. 14468
days	.83	kg. mg.	kg.	mg.	kg.	mg.	kg.	Rg.
Initial	11.8		13.8		8.1		10.2	
-		2.4		2.8		1.6		2.0
7		2.4		2.8		1.6		2.0
က		2.4		2.8		1.6		2.0
4		2.4		2.8		1.6		2.0
'n	6.7	1.9	12.6	2.5	7.4	1.5	9.3	1.9
•		1.9		2.5		1.5		1.9
7	9.5	1.8	12.7	2.5	6.7	1.3	8.8	1.8
<b></b>	8.9	1.8	11.8	2.4	6.4	1.3	4.8	1.7
6		1.8		2.4		1.3		1.7
10		1.8		2.4		1.3		1.7
==		1.8		2.4		1.3		1.7
12	8.2	1.6	12.5	2.5	6.2	1.2	8.6	1.7
13		1.6		1.5		1.2		1.7
14	7.7	1.5	11.2	2.2	5.6	1.1	7.7	1.5
Terminal	7.6		11.5		2.7		8.0	
Wt. Change, kg.	-4.2		-2.3		-2.4		-2.2	

Table No. 1 - Continued

TIME		GR(	OUP NO. 5	GROUP NO. 5 - 160 MG. WR-2823 PER KG. OF BODY WEIGHT	823 PER KG	. OF BODY WE	GHT	
TWEEDVAT	3	14504 00:00	Dog	No. 14515	Dog N	0. 14470	Dog N	Dog No. 14471
days	kg.	kg. mg.	kg.	COMPOUND	Kg.	COMPOUND	M.	COMPOUND
Initial 1	12.1	4.8	10.5	4.2	9.1	, v	9.7	
ପର୍କ୍ଷ	*	444 888	9.6	* * * * * * * * * * * * * * * * * * *	8.0	• • • • • • • *	8.5	 
Wt. Change, kg.			6.0-		-1.1		-1.2	

\* Animal died. \*\* No terminal weight taken.

TABLE NO. 2 - INDIVIONAL HEMATOLOGICAL VALUES PUREBRED BEAGLES RECEIVING MR-2823 (AU 69115) FOR TWO WEEKS INITIAL

		S		9	Jou	3	1 V L H 3	RAND	SEG	FILE HAND SEG LYMPH MONO	MONO	E0	[sASD	
GROUP	AN IMAL NUMBER	ш ×	도 *	45 <b>25</b>	MILLS	1HS	; ; ;	<b>3</b> €	<b>3</b> €	<b>%</b>	<b>3</b> -6	эх	34°	
		<b>z</b> :	51.0	17.7	6.72	12.7	, c c	cc	64 65	28	<b>- 6</b>	۲ ۲	cc	
	14125		49.0	0.1	• C	•	;							
٩	GRAUP MEAN		20.0	17.4	09.9	11.2							,	
~ ~	14251	ヹヹ	49.0	16.4	6.39	13.9	0	0	45 59	44 35	0	11	cc	
₫	GROUP MEAN		48.0	16.4	6.53	11.6								
m m	14366 14389	ΣΣ	48.0 52.0	16.6	6.35	12.5	0 0	cc	60 56	33	9 10	æ 4	cc	
9	GROUP MEAN		50.0	17.1	6.65	14.5								
4 4	14494 M 14502 M	ΣΙ	47.0	15.0	7.95	10.6	00	c c	50	44	4 4	~ ~	co	
3	GRINP MEAN		48.0	15.6	7.30	15.2								
so so	14507 M 14515 M	Z Z	54.0 53.0	18.0	7.62	13.8	<b>c</b>	0 7	56 60	38	4 -	۲ ٪	CC	
d :	GROUP MEAN		53.5	17.9	7.26	12.5								

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
PUREBRED REAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS
WEEK 1

GROUP NUMBER	ANIMAL NUMBER	м ш ×	HCT *	HGB GX	RBC MILLS	WBC	META %	META BAND SEG LYMPH MONO	SEG *	LYMPH	MONO %	EOSIN	EOSIN BASO
	14121	II	47.0	16.0 16.8	6.07 5.87	12.7	00	0 0	58 62	27 28	2 2	13	00
GROUP	MEAN		48.0	16.4	5.97	11.3							
22	14251	ΣI	47.0	16.2 17.0	6.03	13.2 11.1	00	00	56 46	533	e =	ဆင	00
GROUP MEAN	MEAN		48.0	16.6	6.03	12.2							,
m m	14366 14389	ΣΣ	48.0 54.0	16.6 18.5	5.97	10.5	00	00	45	54 40	7 0		00
GROUP MEAN	MEAN		51.0	17.6	5.90	10,5							
44	14494	ΣΣ	51.0 48.0	16.2 16.4	6.55	9.2	00	<b>к</b> 0	60 54	35	0	7 9	00
GROUP MEAN	MEAN		49.5	16.3	7.20	8.7							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEFKS WEEK 2

I W I W O	νu	HCH	H	RBC	3	META	HAND	DIFFE	AAND SEG IYMPH MOND		FOSIN BASO	6AS0
NUMBER	. ×	24	8	MILLS	THS	96 C	94	) 1 34	*	<b>3€</b>	0 8€	*
121	Σ	46.0	16.2	6.07	12.5	0	С	53	44	0	К	С
14125	Σ	44.0	15.3	5.69	11.5	C	С	64	32	0	4	С
MEAN		45.0	15.8	5.88	12.0							
4251	Z		14.8	6.02	10.7	0		49	28	С	7	C
14253 M	Σ	45.0	14.8	5.95	8.6	c	C	32	29	7	4	0
GROUP NEAN		43.0	14.8	5.49	4.6							
14366	Σ	42.0	14.6	5.48	11.5	0	c	58	35	m	4	0
389	Σ	51.0	17.0	6.65	8.9	၁	0	26	4.2	2	С	С
GROUP MEAN		46.5	15.8	6.07	10.2							
14494 M	Σ	51.0	16.8	8.52	& &	0	ĸ	53	39	5	С	0
4502	Σ		16.6	99•9	7.2	0	C	53	38	m	9	C
GREATING MEAN		49.0	16.7	7.59	8.0							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FUR TWO WFEKS INITIAL

GROUP NUMBER	AN IMA NUMBE	νm× 3	PROTHROMBIN SECONDS	COAGULATION MIN SEC	ATION SEC
., , <u>,</u>	14125	ΣΞ	8.6	o 4	27
GROUP	MEAN		8.0	4	21
2 2	14251 14253	ΣΣ	7.9	m 4	32 02
GROUP	MEAN		7.7	3	47
m m	14366	ĮI	7.8 7.6	1 4	37
GROUP	MEAN		7.7	2	23
4 4	14494	ΣΣ	8.2	2	60
GROUP	MEAN		7.8	2	52
2 2	14507 14515	ΣΣ	7.4	~	ND 42
GROUP	MEAN		7.5	2	42

ND - NO DETERMINATION

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS WEEK 1

PROTHROMBIN SECONDS	7.8	7.7	7.6 7.5	7.6	7.4	7.3	7.3	7.3
νшх	ΣΣ		ΣI		ΣΣ		II	
ANIMAL NUMBER	14121 14125	MEAN	14251 14253	MEAN	14366 14389	MEAN	14494	MEAN
GROUP NUMBER		GROUP	22	GROUP	МM	GROUP	44	GROUP MEAN

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES PUREBRED REAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WFEKS WEEK 2

ATION SEC	36 45	41	53 18	36	20	03	30	37
COAGULATION MIN SEC	4 0	S	5.50	જ	8 7	80	4 0	70
PROTHROMBIN SECONDS	6.6 7.1	6*9	6.5	9*9	7.1 6.6	6.9	6.5	6.5
νшх	ΣΣ		ΣΣ		ΣΣ		ΣΣ	
AN IMAL NUMBER	14121	MEAN	14251 14253	MEAN	14366 14389	1EAN	14494	FAN
GROUP	~~	GROUP MEAN	2 2	GROUP	mm	GROUP MEAN	4 4	GROUP MEAN

100 Sept. 100 Se

TABLE ND. 2 - INDIVIDUAL HEGATOLOGICAL VALUES PUREBRED REAGLES RECFIVING WR-2823 (AU 69115) FOR TWO WFEKS INITIAL

diffida	N M M	voπ	Į	HGB	RAC	MBC	META	BAND	OIFFE SEG	DIFFERENTIAL META BAND SEG LYMPH MON	MONO	EOSIN	BASO
NUMBER	NUMBER		<b>3</b> €	8	MILLS	THS	3€	9€	<b></b> €	<b>3</b> -6	8€	34	%
-	16333	ц	52.0	18.0	96.9	11.9	С	С	53	41	ю	т	0
	14348	. ц	54.0	18.2	7.72	15.6	0	0	39	61	0	C	C
GROUP MEAN	MEAN		53.0	18.1	7.34	13.8							
^	14355	u	45.0	15.8	6.25	12.1	c	0	57	43	0	С	0
· ~	14457	ட	50.0	16.4	6.22	13.8	0	~	53	39	7	S.	0
GROUP MEAN	MEAN		47.5	16.1	6.24	13.0							
ď	14417	_	56.0	19.6	7.76	11.4	C	С	51	46	С	بر	С
	14435	<u>. u</u>	49.0	17.0	6.41	9.2	0	0	63	31	c	9	С
GROUP MEAN	MEAN		52.5	18.3	7.09	10.3							
4	14458		47.0	15.0	6.38	12.5	C	ĸ	50	41	æ	m	С
. 4	14468	<u>u</u>	51.0	16.4	6.39	10.8	С	-	64	32	7	-	0
GROUP MEAN	MEAN		49.0	15.7	6.39	11.7							
r r	14470 14471	ш ш	51.0 50.0	16.8 16.8	6.72	12.2	<b>c</b> c	10	40 63	53 36	0 7	·+ ~	0
GROUP MEAN	MEAN		50.5	16.8	6.75	12.4							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS

		S					1		į	1			
GROUP	ANIMAL R NUMBER	шх	HCT %	HGB G%	RBC MILLS	WBC	META %	BAND #	UIFFE SEG	META BAND SEG LYMPH MONO % % % % % %	MONO %	EOSIN	BASO
	14333 14348	<b>L</b> L	54°0 50.0	18.5 16.8	6.35	12.3	00	00	49	45 53	2	<b>~</b> 4	00
GROUP	GROUP MEAN		52.0	17.7	6.47	13.6					ŀ	-	<b>S</b>
2 2	14355	ш. ш.	48.0	16.4 16.2	6.44	12.7	00	~0	56 41	42 51	<b></b> (c)	0 10	00
GROUP	MEAN		48.0	16.3	6.28	12.9					ì	١	;
mm	14417	44	55.0 54.0	19.2 18.9	6.44 6.71	11.18.8	00	0 0	65 64	29 31	~ ~	<b>∾</b> κ	00
GROUP MEAN	MEAN		54.5	19.1	6.58	10.0				•	J	1	
4 4	14458 14468	щ.	51.0 58.0	17.2 20.0	9.06	7.7	CC	2	63 63	30 32	~ ~	c -	00
GROUP MEAN	MEAN		54.5	18.6	76 • 2	9.2					1	1	•

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS WEEK 2

GROUP	GROUP ANIMAL NUMBER NUMBER	νшх	HC #	нсв 6 <b>2</b>	RBC MILLS	WBC THS	META %	BAND **	DIFFE SEG *	DIFFERENTIAL META BAND SEG LYMP!' MONO % % % % % %	MONO %	FOSIN	BASO %
	14333 14348	டிடி	52.0 46.0	18.2	6.71 6.55	11.7	CC	0 0	59	36 53	<b>-</b> 0	4 0	c o
GROUP MEAN	MEAN		0.64	17.3	6.63	11.7							
~ ~	14355	டட	41.0	14.2	5.54 5.53	10.3	<b>0</b> 0	10	56 48	39 48	7	~ m	cc
GROUP MEAN	MEAN		42.5	14.4	5.54	10.0							
m m	14417 F 14435 F	டட	53.0 50.0	17.5 17.7	7.27	12.4 9.1	00	0	73	24 29	0 7	<b>∼</b> 4	00
GROUP MEAN	MEAN		51.5	17.6	6.91	10.8							
44	14458 F 14468 F	шш	50.0 53.0	17.2	6.71 7.00	10.7 9.7	cc	00	64 64	30	0	2 -	00
GRINDP NEAN	PIEAN		51.5	17.7	6.86	10.2							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR THO WFEKS INITIAL

77	25	48	04 16	10	34	01	25 15	50	58 20	ć
-4	3	7	2.2	2	w 0	æ	4 W	ю	m m	ć
8.0	7.8	6.7	7.8 7.6	7.7	7.6 7.8	7.7	7.5	7.6	7.4	r
ů.	т.		டிய		டிடி		டிடி		டிட	
14333	14348	MEAN	14355 14457	MEAN	14417	MEAN	14458 14468	MEAN	14470 14471	200
	-	GROOP	8 8	GROUP	mm	GROUP !	4 4	GROUP	rz rz	
	F 8.0 1	F 8.0 1 F 7.8 3	14333 F 8.0 1 14348 F 7.8 3 MEAN 7.9 2	14333 F 8.0 1 14348 F 7.8 3 MEAN 7.9 2 14355 F 7.8 2 14457 F 7.6	14333 F 8.0 1 14348 F 7.8 3 MEAN 7.9 2 14457 F 7.8 2 MEAN 7.7 2	14333 F 8.0 1 14348 F 7.8 3  MEAN 7.9 2 14457 F 7.8 2  MEAN 7.7 2  14417 F 7.6 3  14435 F 7.6 3	14333 F 8.0 1 14348 F 7.8 3  MEAN 7.9 2 14355 F 7.8 2 14457 F 7.6 2  MEAN 7.7 2  MEAN 7.7 3	14333 F 8.0 1 14348 F 7.8 3  MEAN 7.9 2 14355 F 7.8 2 14457 F 7.6 2  14417 F 7.6 3  MEAN 7.7 3  MEAN 7.7 3  MEAN 7.7 3	14333 F 8.0 1 14348 F 7.8 3  MEAN 7.9 2  14355 F 7.8 2  14457 F 7.6 2  14417 F 7.6 3  MEAN 7.7 3  MEAN 7.7 3  MEAN 7.7 3  MEAN 7.5 4  MEAN 7.5 4  MEAN 7.6 3	14333 F 8.0 1 14348 F 7.8 3  MEAN 7.9 2  14455 F 7.8 2  14457 F 7.6 2  14417 F 7.6 3  MEAN 7.7 2  MEAN 7.7 3  MEAN 7.7 3  MEAN 7.7 3  MEAN 7.6 3  14458 F 7.5 4  MEAN 7.6 3  MEAN 7.6 3  MEAN 7.6 3

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS WEEK 1

PROTHROMBIN SECONDS	7.7	7.6	7.3	7.3	7.3	7.3	6.9	7.0
νшх	<b>LL 1</b> L		щц		டிட		<b>u.</b> u.	
ANIMAL NUMBER	14333 14348	MEAN	14355	MEAN	14417	MEAN	14458 14468	MEAN
GROUP	11	GROUP MEAN	88	GROUP	m m	GROUP MEAN	44	GROUP MEAN

Section 2

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEFKS WEEK 2

	DMBIN COAGULATION IDS MIN SEC	6 07 4 30	5 19	6 25	9 42	7 14	00 9	5 12 7 00	•
3	PROTHROMBIN SECONDS	F 7.3 F 6.8	7.1	F 7.1 F 6.5	6.8	F 7.0 F 6.9	7.0	F 6.0	
X F F F K	S ANIMAL E NUMBER X	14333 F 14348 F	MEAN	14355 F 14457 F	MEAN	14417	MEAN	14458	
	GR (1UP NUMB ER		GROUP MEAN	2.2	GROUP	m m	GROUP	4 4	

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES PUREURED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS INITIAL

ALK.PHOS K-A.UNITS	7.0	7.5	8.1 11.0	9.6	8.0 9.8	8.9	11.9	11.2	10.0 11.5	10.8
SGPT R-F.	37.5	32.8	28.0 23.0	25.5	28.0	28.5	23.0	23.0	25.0	25.5
BUN MG%	14.0 11.0	12.5	10.0 10.0	10.0	10.0	10.01	11.0	11.3	9.0	11.0
GLUCUSE MG%	100.0	102.0	95.0 101.0	0.86	103.0 90.0	96.5	106.0 110.0	108.0	104.0 108.0	106.0
νш×	ΣΣ		ΣΣ		ΣΣ		ΞΣ		ΣΣ	
ANIMAL NUMBER	14121 14125	MEAN	14251 14253	MEAN	14366	MEAN	14494	MEAN	14507 14515	MEAN
GROUP		GROUP	2 %	GROUP	мM	GROUP	4 4	GROUP	יט יט	GROUP

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS WEEK 1

gnoad	142	SI	3303113	9	1033	SOLIO VIA
NUMBER		<b>u</b> ×	MG%	₩ ₩ ₩	8-F.	K-A.UNITS
_	14121	I	101.0	13.0	39.0	4.6
1	14125	Ľ	103.0	8.5	32.5	7.8
GROUP	MEAN		102.0	10.8	35.8	8.6
~	14251	Σ	98.0	12.0	31.0	7.9
2	14253	Σ	0.86	11.5	28.0	0.6
GRAUP	MEAN		0.86	11.8	29.5	8.5
m	14366	Σ	130.0	13.0	39.0	8.2
6	14383	Σ	121.0	21.0	37.5	1.6
скоир 1	MEAN		125.5	17.0	38.3	0.6
4	14494	Σ	122.0	57.0	26.0	13.6
4	14502	Σ	115.0	19.5	25.0	12.3
GROUP	MEAN		118.5	38.3	25.5	13.0

TABLE NO. 3 - IMPIVIDUAL BLOOD CHEMISTRY VALUES
PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WFFKS
WEEK 2

Ş	15 [TS	<b>~</b> !	~	_	_	<b>~</b> 1		10	•	<b>0</b> 1	.•	~	
2 14	ALK.PHUS K-A.UNITS	5.6	8.9	6.0	0.9	8.2	7.1	5.5	<b>9</b>	6.2	11.4	6.3	
+ 4 4	R-F.	39.0	34.0	36.5	46.0	37.5	41.8	31.0	34.0	32.5	28.0	37.5	
	W CN	12.5	11.0	11.8	14.0	18.0	16.0	14.0	18.0	16.0	108.0	17.0	
	6L UC 113E MG%	108.0	120.0	114.0	100.0	118.0	103.0	109.0	95.0	102.0	155.0	142.0	
n L	u ×	Σ	Σ		Σ	Σ		Σ	Σ		Σ	Σ	
	NUMBER	14121	14125	MEAN	14251	14253	MEAN	14366	14389	MEAN	14494	14502	
011000	NUMBER	-	7	GROUP	~	7	GROUP	3	6	GROUP	4	4	

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES PUREBRED BEAGLES RECFIVING WR-2823 (AU 69115) FOR TWO WFEKS INITIAL

T ALK.PHUS K-A.UNITS	0 14.4 0 14.4	5 12.3	0 13.3 5 9.1	8 11.2	6 6	2	0 14.2 0 9.9	5 12.1	0 10.2 0 7.8	0
SGPT R-F.	23.0 34.0	28.5	26.0	31.8	31.0 22.0	26.5	28.0	25.5	25.0 25.0	25.0
BUN MG%	12.0 14.0	13.0	17.5 12.0	14.8	10.0	10.0	9.0 10.0	6.6	9.0 10.0	6.8
GLUCUSE NG%	106.0	102.5	110.0 112.0	1111.0	98.0 105.0	101.5	107.0 100.0	103.5	102.0 98.0	100.0
NШX	щщ		u. u.		<b>u</b> u		u u		u u	
ANIMAL NUMBER	14333 14348	MEAN	14355 14457	MEAN	14417	MEAN	14458 14468	MEAN	14470	MEAN
GROUP NUMBER	1	GROUP	2 2	GROUP	m m	GROUP	4 4	GROUP	ינה ינה	GROUP

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS WEEK 1

			:			
GROUP	ANIMAL	SШ	GLUCOSE	BUN	SGPT	ALK.PHOS
NUMBER	NUMBER	×	¥ 20 ¥	¥0¥	X-X.	K-A.UNITS
-	14333		116.0	8.0	26.0	6.6
_	14348	u.	113.0	14.0	37.5	12.4
GROUP	MEAN		114.5	11.0	31.8	10.9
7	14355	<b>L</b>	111.0	21.0	25.0	10.0
~	14457	ш	115.0	14.0	37.5	0.6
GROUP	MEAN		113.0	17.5	31.3	6.5
ю	14417	u.	0.46	15.0	26.0	7.9
3	14435		105.0	21.0	34.0	8.0
GROUP	MEAN		66.5	18.0	30.0	8.0
4	14458	u.	98.0	29.5	28.0	17.3
4	14468	u.	125.0	20.0	36.0	11.2
GROUP	MEAN		111.5	24.8	32.0	14.3

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUFS PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WFEKS WEEK 2

GROUP	ANIMAL	S III	GLUCOSE	RUN	SGPT	ALK.PH0S
NUMBER	NUMBER	×	₩C%	<b>WC%</b>	R . F.	K-A.UNITS
	14333	ட	112.0	11.0	32.5	7.5
	14348	u.	115.0	14.0	35.5	130.0
~	MEAN		113.5	12.5	32.5	8.89
	14355	ų.	120.0	20.0	31.0	7.9
	14457	u.	115.0	13.0	37.5	8.2
~	MEAN		117.5	16.5	34.3	8.1
	14417		115.0	21.0	32.5	7.5
	14435	щ	130.0	18.0	32.5	5.9
_	MEAN		122.5	19.5	32.5	6.7
	14458	Œ.	126.0	30.3	31.0	10.0
	14468	u.	139.0	21.0	37.5	8.2
~	GROUP MEAN		132.5	25.7	34.3	9.1

131

193-406

SPERM	MANY MANY	FEW MANY			
BACT SI	MANY MANY	MANY	MANY	MANY MANY	M A N Y M A N Y
NDINGS CRYS	M A A A A A A A A A A A A A A A A A A A	MAR V X	MANY	MANY I	MANY P
MICROSCOPIC FINDINGSBERM BC WBC EPITH AMORPH CRYS BACT SPERM	MUCH	мисн	мпсн	MUCH	мосн
CROSC( EP1TH	1-3 6-8	3-5	4-6 8-10	2-4	3-5
W.B.C	8-10 16-18	6-8 8-10	12-14 3-5	6-8 6-8	6-8
RBC	13	2-4	1-3		4-6 1-3
VOL.	135	65 135	75 85	155 135	55 95
078 000	cc	00	cc	0 0	CC
BILI- RUBIN	0 0	<b>-</b> 0	0 0	0 0	<b>-</b> 0
PRO- TEIN	1				
ACE- TUNE	cc	00	0 0	0 0	0 0
SU- GAR	00	00	0 0	00	CC
SP.GR.	1.050	1.06+	1.045	1.050	1.046
ΔI	~ ~	<b>ω ω</b>	7	8 4	9
$\infty$ m $\times$	ΣΣ	ΣΣ	ΣΣ	ΣΣ	ΣΣ
AN IMAL NUMBER	14121 14125	14251 14253	14366 14389	14494	14507 14515
GROUP NUMBER	~~	~ ~	m m	44	N W

TABLE NO. 4 - URINE ANALYSIS PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS WEEK 1

SPERM	FEW MANY	MANY	N33	
HACT	MANY MANY	MANY MANY MANY MANY	MANY MANY	AA MA
NDI NGS CRYS	MANY MANY	MANY		я Э
MICROSCOPIC FINDINGSBRC WRC EPITH AMORPH CRYS BACT SPERM	MUCH	МОСН	мисн	8-10 МИСН 8-10 МИСН
CROSCO EPITH	2-4	1-3	4 - 6 4 - 6	8-10 8-10
WBC	8-10 20-30	8-10	8-10 TNTC 10-12	TNTC
RBC		1-2	8-10	8-10
vol.	127	119	175	121 397
	00	00		<b>⊢</b> ⊢
PRO- BILI- OCC TEIN RURIN HLD	1	c o	0	cc
PRO- TEIN				~ ~
SU- GAR	0	cc	o <b>c</b>	0 0
SP.GR.	1.044	1.037	1.024	1.038
a I	& &	יט יט	φ	\$ 5
$\sim$ $\pm$ $\times$	zz	ΣΣ	ΣΣ	ΣΣ
AM IMAL NUMRFR	14121	14251	14366	14494 14502
GROUP NUMRER	<b></b>	~ ~	er m	4 4

- URINE ANALYSIS

				PURER	RED	BEAGL	ES REC	ECE IVI WEEK	ING WR	1-2823	( Atl 69	1151	PUREBRED BEAGLES RECEIVING WR-2823 (AN 69115) FOR TWO WEEKS WEEK 2	WEEKS		
GROUP NUMBER	AN IMAL NUMBER	αux	ΦI	SP.GR.		PRG- TEIN	SU- PRO- BILI- OCC GAR TEIN RUBIN BLD VOL.	00CC RLD	·vol.	RBC	WBC	ICROSC( EPITH	MICROSCOPIC FINDINGSBE BC WBC EPITH AMORPH CRYS BACT SPERM	NDI NGS CRYS	BACT	SPERM
1 1	14121	ΣΣ	æ <b>~</b>	1.042	00		<b></b>	00	130		6-8 18-20	2-4	МОСН	X X X X X X X X X X X X X X X X X X X	MANY MANY	FEW MANY
^ ^	14251 14253	ΣΣ	~ ~	1.024	00	~~	co	1 0	115	115 3-5 195	1-3 8-10	2-4	MUCH	MANY MANY	MANY MANY MANY HANY	МАМУ
m m	14336	ΣΣ	20.00	1.032	0	<b></b>	c c	0	150	150 1-2 110 TNTC	2-4	1-3	мисн	FEW MANY	MANY MANY	MAM
4 4	14494	ΣΣ	8 ~	1.047 0 1.018 0	00		cc		75	75 10-12 20-25 225 TMTC	20-25	10-15	MUCH 10-15 MUCH	M A N N N N N N N N N N N N N N N N N N	MANY MANY MANY MANY	H H H

TABLE NO. 4 - URINE ANALYSIS PUREBRED REAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS INITIAL

SPERM					
S BACT	MANY MANY	MANY MANY	MANY MANY	MANY	MANY MANY
NDI NG	MANY MANY	MANY MANY	FEW MANY	FEW MANY	HANY
MICROSCOPIC FINDINGS	LITTLE MUCH	MUCH	LITTLE MUCH	MUCH	MUCH
ICROSC EPITH	4- <del>6</del>	2-4	1-3 6-8	8-10	4-6
M]	2-4 10-12	2-4 TNTC	12-14	10-12 12-14	2-4 12-15
RBC					
vol.	115 50	65	135 86	75	105 115
018 000	cc	00	c c	cc	CO
RILI- RUBIN	0 0	00	<b>3</b> 0	0 0	<b>0</b> 0
PRN- TEIN	7 7		1		
ACE- TUNE	o c	00	0 0	cc	ဝပ
SU- GAR	00	00	0 0	CO	c o
P H SP.GR. GAR	1.06+	1.000	1.000	1.050	1.040
σI	2	5 ~	6	N N	۲ ر
SШX	шш	u. u.	14. 14.	<b>LE LE</b>	шш
AN I MAL NUMBER	14333	14355 14457	14417	14458 14468	14470
GROUP		~ ~	m m	4 4	ሌ W

TABLE NO. 4 - URINE ANALYSIS PUREBRED BEAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WEEKS WEEK 1

5	-			
7010	-			
S	MANY	MANY	HANY MANY	AANY MANY
NDING	MANY	MANY FFW	3 U	FEW
NICROSCOPIC FINDINGS	MUCH	иосн МОСН	MUCH	MUCH
CROSC EPITI	2-4 6-8	1-3	2-4	1-3 6-8
NI WBC	6-8 TNTC	8-10 10-12	8-10	8-10 10-12
RBC		7-6		
VOL.	73 88	137 59	199 167	193 135
OCC BLD	00	F 5	<b>၁</b> o	0 0
BILI- OCC RUBIN BLD	CO	0 0	0 0	0 0
PKC- TEIN	1	1		
SU- GAR	ငင	0 0	СС	0 0
SP.GR.	1.038	1.024 1.058	1.022	1.026
ıπ	5 &	δ <sub>1</sub> 0	\$ 9	in in
νшх	шш	ஈ ஈ	யம	ш ш
AN I MAL NUMBER	14333 14348	14355	14417	14458 14468
GROUP		2 2	m m	4 4

TABLE NO. 4 - URINE ANALYSIS
PUREBRED REAGLES RECEIVING WR-2823 (AU 69115) FOR TWO WFEKS
WEEK 2

SPERM				
BACT	MANY MANY	MANY	MANY MANY	MANY
DINGS	MANY MANY	MANY	MANY	MANY
MICROSCOPIC FINDINGSBERM BC WBC EPITH AMORPH CRYS BACT SPERM	MUCH	MUCH	мисн мисн	MUCH
CROSC( EPITH	4-6 3-5	4-6	20-23 10-12 MUCH TNTC 20-25 MUCH	TNTC 10-12 MUCH 8-10 12-14 MUCH
WBC	6-8	2-4	20-23 TNTC	TNTC 8-10
RBC	4-6			
VOL.	102 125	185 125	335 175	110 190
	0 +	<b>⊢</b> ⊢		<b></b>
SU- PRN- BILI- UCC GAR TEIN RURIN BLU	0	o C	0 0	cc
PRO-	~ <b>-</b>	0 -		1
	0	oc	cc	00
SP.GR.	1.042	1.023	1.014	1.022
ΔI	~ ~	សស	<b>~</b> 8	2 2
УШХ	டிட	T T	<b></b>	டிட
ANIMAL NUMBER	14333 14348	14355 1445 <i>7</i>	1441 <i>7</i> 14435	14458 F 14468 F
GROUP NUMBER	<b></b>	~ ~	m m	4 4

TABLE NO. 5 - TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, AND ORGAN/BODY WEIGHT RATIOS

SPECIES AND STRAIN - BEAGLE DOGS INTERVAL - TERMINAL MATERIAL - WR-2823 ROUTE OF ADMINISTRATION - INTRAVENOUS

MALES - GROUP 1

EN RATIO PCT	0.3423	0.3506			/31
SPLEEN WEIGHT 6	35.600 42.000	38.800			
ER RATIO PCT	2,4134 2,6324	2,5229	ES RATIO PCT	0.2201	0.2306
LIVER WEIGHT G	251,000 308,000	279.500	TESTES WEIGHT	22.900 28.200	25.550
RT RATIO PCT	0.9038 0.8316	0.8677	IALS RATIO PCT	0.0104	9600.0
HEART WEIGHT G	94.000 97.300	95.650	ADRENALS Weight RA	1.090	1.050
OID RATIO PCT	0.0089	0.0088	IEYS RATIO PCT	0.4538	0.4739
THYROID WEIGHT R.	0.930	0.975	KIDNEYS Weight R G	47.200 57.800	52,500
TERM. BODY Weight Kg	10.40	11.05	TERM. BODY Weight Kg	10.40	11.05
ANIMAL NO.	14121 14125	MEAN	AN I MAL NO.	14121	MEAN

TABLE NO. 5 - CONTINUED

## MALES - GROUP 2

EN RATTO	PCT	0.2583	0.2721				138
SPLEEN WEIGHT	9	26.600	24.150				
VER RATIO	PCT 2 54.74	3.1397	2.8437	ES	RATIO PCT	0.1869	0.2025
LIVER WEIGHT	6 214-000	292.000	253.000	TESTES	WE IGHT G	15.700	18.000
HE ART RATIO	0.7559	0.6978	0.7269	VAL S	RAT 10 PCT	0.0096	0.0103
HE IGHT	63.500	64.900	64.200	ADRENAL S	WEIGHT G	0.810 1.030	0*650
RDID RATIO PCT	0.0170	0.0096	0.0133	_	PCT	0.5797 0.5236	0.5517
THYRO Weight G	1.430	0.900		KIONE	6	<b>48.700</b>	48.700
TERM. BODY Weight Kg	8 .0	9.30 8.85		TERM. BODY WEIGHT	KG	8.40 9.30	8.85
AN IMÁL NO.	14251	MEAN		AN I MAL NO.	7	14251 14253	MEAN

TABLE NO. 5 - CONTINUED

MALES - GROUP 3

RATIO PCT	0.2059	0.2007		13	9
SPLEEN WEIGHT RA	17,300	18.620			
ER RATIO PCT	2,4285	2,2633	ES RATIO PCT	0.2607	0.2234
LIVER WEIGHT RA	204.000 214.000	209.000	TESTES WEIGHT 6	21.900 19.000	20.450
RT RATIO PCT	0.6833	0869*0	IALS RATIO PCT	0.0110	0.0115
HEART WEIGHT G	57.400 72.700	65.050	ADRENALS Weight RA	0.930	1.080
DID RATIO PCT	0.0071	0.0082	VEYS RATIO PCT	0.5071 0.5088	0.5079
THYROI WEIGHT G	096.0	0.179	KIDNEYS Weight R G	42.600 51.900	47.250
TERM. BODY Weight Kg	8.40 10.20	9•30	TERM. BODY Weight Kg	8.40 10.20	9 • 30
ANIMAL NO.	14366 14389	MEAN	ANIMAL NO.	14366	MEAN

TABLE NO. 5 - CONTINUED

# MALES - GROUP 4

ANIMAL	TERM. BODY	THYROID	010	HEART	RT	LIVER	E. S.	SPLEEN	2
ON	WE IGHT KG	WEIGHT G	RAT10 PCT	WE1GHT G	RAT 10 PCT	WEIGHT G	RATIO PCT	WEIGHT 6	RAT10 PCT
14494	7.60	069.0	0.0000	57.500	0.7565	227.000	2.9868	21.600	0.2842
14502	11.50	0.870	0.0075	81.200	0901.0	312,000	2.7130	40.600	0.3530
MEAN	9.55	0.779	0.0083	69,350	0.7313	269,500	2.8499	31.100	0.3186
ANIMAL	TERM. BODY	K I DNE	IEYS	ADRENAL S	AL S	TESTES	ËS		
0	WEIGHT KG	WEIGHT G	RAT 10 PCT	WEIGHT G	RAT 10 PCT	WEIGHT G	RATIO PCT		
14494	7.60	47.000	0.6184	1.120	0.0147	15.700	0.2065		
14502	11.50	59.100	0,5139	1.210	0.0105	29.300	0.2547		
MEAN	9.55	53.050	0.5661	1.165	0.0126	22.500	0.2306		14

TABLE NO. 5 - CONTINUED

MALES - GROUP 5

ANIMAL ND.	TERM. BODY Weight Kg	THYRI WEIGHT G	RATIO PCT	HEART WEIGHT RATIO	RT RATIO PCT	LIVER WEIGHT RATIO	ER RATIO	SPLEEN WEIGHT RATIO	EN RATIO
* 14515	09*6	0-850	0.0088	71,300 0.7427	0.7427	398.000 4.1458	4.1458	97.500	G PCT 97.500 1.0156
ANIMAL NO.	TERM. BODY Weight Kg	KIDNEYS WEIGHT RA	HEYS RATIO PCT	ADREN Weight G	ADRENALS EIGHT RATIO W G PCT	TESTES WEIGHT RATIO	ES RATIO PCT		
14515	09*6	87.600	0.9125	1.350	1.350 0.0140	13.900 0.1447	0.1447		

\* Weight for Dog No. 14504 was omitted due to technical error.

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FEMALES - GROUP 1

ANIMAL NO.	TERM. BODY Weight Kg	THYROID WEIGHT R G	010 RATIO PCT	HEART WEIGHT G	RT RAT10 PCT	LIVER WEIGHT G	ER RATIO PCT	SPLEEN WEIGHT RA G P	EN RATIO PCT
14333	9.60	0.580	0.0060	70.900	0.7385	211.000 250.000	2.1979	23.000 23.800	0.2395
MEAN	8 • 00	0.775	0.0105	99***	0.8528	230.500	3.0520	23.400	0.3057
ANIMAL NO.	TERM. BODY Weight Kg	KIDNEYS Weight R	EYS RATIO PCT	ADRENALS WEIGHT R/	ALS RATID PCT	OVARIES WEIGHT R. G	IES RATIO PCT		
14333 14348	9.60	51.100 36.300	0.5322 0.5671	1.050	0.0109	0.900	0.0093		
MEAN	8 00	43.700	0.5497	1.005	0.0129	0.830	0.0106		142

TABLE NO. 5 - CONTINUED

FEMALES - GROUP 2

ANIMAL	TERM. BODY	THYROID	010	HEART	RT	LIVER	ER	SPLEEN	EN
°ON	WE I GHT KG	WEIGHT 6	RAT 10 PCT	WEIGHT G	RAT 10 PCT	WEIGHT G	RATIO PCT	WE I GHT G	RAT 10 PCT
14355	7.00	0.090	0.0057	56.800 57.100	0.8114	164.000 195.000	2.3428	16.800 23.200	0.2400
MEAN	7.15	0.245	0.0034	56.950	0.7968	179.500	2.5070	20,000	0.2789
AN IMAL NO.	TERM. BODY Weight Kg	KIDA WEIGHT G	KIDNEYS T RATIO PCT	ADRENAL S Weight RA G	IAL S RAT IO PCT	DVAR Weight G	OVARIES IT RATIO PCT		
14355	7.00	30.800	0.4400	0.950	0.0135 0.0117	0.800	0.0114		
MEAN	7.15	33,300	0.4652	0.904	0.0126	0.750	0.0105		143

TABLE NO. 5 - CONTINUED

FEMALES - GROUP 3

ANIMAL ND.	TERM. BODY Weight Kg	THYRD WEIGHT G	RDID RATIO PCT	HEART WE IGHT	IRT RATIO PCT	LIVER WEIGHT	VER RATIO PCT	SPLEEN WEIGHT	ш
14417	7.60	1.150	0.0151	69.000	0.9078	209.000 103.000	2.7500 2.1458	29.70U 12.900	
MEAN	6.20	0.730	0.0107	59.450	0.9737	156.000	2.4479	21,300	
ANIMAL NO.	TERM. BODY Weight Kg	KIDNEYS WEIGHT R.	VEYS RATIO PCT	ADRENALS WEIGHT RA	ALS RATIO PCT	OVARIES WEIGHT R.	RATIO PCT		
14417	7.60	36.700 26.200	0.4828 0.5458	0.980	0.0128	0.770	0.0101		
MEAN	6.20	31.450	0.5143	0.875	0.0144	0.635	0.0102		

TABLE NO. 5 - CONTINUED

FEMALES - GROUP 4

ANIMAL	TERM. BODY	THYROID	010	, un	HE AD T	•	į		
2	WE I GHT KG	WEIGHT G	RAT 10 PCT	WE 16HT 6	RATIO PCT	LIVER WEIGHT P	/ER RATIO PCT	SPLEEN WEIGHT	EN RAT10 PCT
14458 14468	5.70 8.00	0.730	0.0128	54.700 63.200	0.9596	137.600	2.4140	18,700	0.3280
MEAN	6.85	0.735	0.0110	58,950	0.8748	69.759	1.2190	22.200	0.3246
AN IMAL NO.	TERM. BODY Weight Kg	KIDNE WE <i>igh</i> t G	EYS RATIO PCT	ADRENALS WEIGHT RA G P	ALS RATIO PCT	OVARIES Weight RA	IES RATIO PCT		
14458	5.70 8.00	33.900 46.900	0.5947	1.000	0.0175	0.450	0.0078		
MEAN	6.85	40.400	0.5904	1,225	0.0178	0.600	0.0086		

TABLE NO. 5 - CONTINUED

FEMALES - GROUP 5

ANIMAL NO.	TERM. BODY Weight Kg	THYROI WEIGHT G	OID RATIO PCT	HEART WEIGHT G	RT RATIO PCT	LIVER WEIGHT RA G	FR RATIO PCT	SPLEEN WEIGHT RA	EN RATIO PCT
14470	8.00 8.50	0.920	0.0115	53.300 72.100	0.6662	328.000 373.000	4.1000 4.3882	95.800	1.1975
MEAN	8.25	0.825	0.0100	62.700	0.7572	350,500	4.2441	85.400	1.0399
AN IMAL NO.	TERM. BODY Weight Kg	KIDNEYS Weight R G	IEYS RAT10 PCT	ADRENALS Weight RA G	IALS RATIO PCT	OVARIES WEIGHT R/ G	IES RATIO PCT		
14470	8.50	58.400	0.7300	1.070	0.0133	0.700	0.0087		
HEAN	8.25	906*+9	0.7850	1.180	0.0142	0.764	0.0092		l

#### HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: December 10, 1969

Material:

WR 2721

Subject:

REPORT NO. 25

Four-Week Oral Toxicity Study - Monkeys

Project No. 193-407

#### SUMMARY

WR 2721 was administered orally by gastric intubation daily for four weeks to three groups of four male rhesus monkeys at dosage levels of 8.3, 25.0, and 75.0 mg/kg/day. A fourth group served as a control and received daily doses of the vehicle. Criteria evaluated for compound effect included general appearance and behavior, appetite, elimination, body weight changes, clinical studies, organ weights and organ/body weight ratios, and gross and microscopic pathology.

Body weights in control animals and in animals at the low and intermediate test levels were generally maintained or increased. Animals at the high test level lost from 5% to 14% of their initial weight.

Clinical studies revealed slightly increased prothrombin time values at two weeks for one control monkey, three intermediate level monkeys, and four high level monkeys. The remaining hematological values, the biochemical values, and the results of urine analyses generally were within normal limits and were comparable to values for control animals.

Evaluation of the remaining criteria including microscopic examination of tissues indicated no compound-related effects.

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# INTRODUCTION

The purpose of this study was to characterize and evaluate the subacute oral toxicity of WR 2721 in rhesus monkeys. The study was initiated on September 15, 1969, and was terminated on October 16, 1969.

#### MATERIAL

Identification WR 2721.

<u>Description</u> Fine, white powder with a faint odor.

Receipt Date June 7, 1968.

Purity Assumed 100% active.

## **METHODS**

# Experimental Animals

preed: Rhesus monkeys.

Number: Sixteen males.

Body Weight (At Initiation): 2.0 to 2.8 kg.

Housing: Individually in metal cages.

Diet: Purina Monkey Chow, apples five times a week, and water ad libitum.

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## Animal Groups and Dosage Levels

Group No.	No. of Monkeys	Material	Dosage Level mg/kg/day
1 (control)	4	distilled water	75.0
2	4	WR 2721	8.3
3	4	WR 2721	25.0
4	4	WR 2721	75.0

# Compound Preparation and Administration

The test compound and the vehicle control were prepared weekly using the body weight at the end of a given week for the following week's dose regimen. All control and test monkeys received their dose by oral intubation daily for four weeks.

All animals received their appropriate dosages for three days in the fifth week.

#### Observations and Records

Daily: Appearance, behavior, appetite, elimination, and signs of compound effect.

Weekly: Body weights.

## Clinical Studies

Performed: Twice initially and at two and four weeks.

Hematology: Hematocrit and hemoglobin determinations, erythrocyte counts, total and differential leukocyte counts, and prothrombin time.

Biochemistry: Determinations of fasting blood sugar, blood urea nitrogen, total bilirubin, direct bilirubin, serum glutamic-pyruvic transaminase, alkaline phosphatase, total protein, total albumin, albumin/globulin ratio, and

creatinine. In addition, blood urea nitrogen, total bilirubin, serum glutamic-pyruvic transaminase, and creatinine were performed 24, 48, and 72 hours following the first dose.

Urine Analyses: Specific gravity, pH, protein, sugar, bilirubin, occult blood, volume, and microscopic examination.

## Ophthalmologic Examination

Performed: Initially and terminally.

# Terminal Studies

Necropsies: Performed on all monkeys sacrificed after four weeks of oral intubation.

Organ Weights: Thyroid, heart, liver, spleen, kidneys, adrenals, testes, and prostate.

### Tissues Preserved:

In 10% Neutral Buffered Formalin - Brain, pituitary, thoracic spinal cord, thyroid, lung, heart, liver, gallbladder, spleen, kidney, adrenal, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testes, prostate, rib junction, bone marrow, and nerve with muscle.

In Alcoholic Formalin - Eyes.

# Histopathological Examination

From Control and High Level Monkeys: Sections of all tissues listed above.

From Low and Intermediate Level Monkeys: Sections of liver and kidney.

#### RESULTS

## Appearance, Behavior, and Signs of Compound Effect

No remarkable pharmacotoxic signs attributable to the test material were observed during the course of the study. Episodes of diarrhea were noted in most of the monkeys in all groups including the controls, but the animals responded within two or three days to the standard laboratory treatment. Other incidental observations included emesis (one control), mucus in feces (one control), piloerection (one control, two low level animals, and one high level animal), and moderate anorexia (one intermediate level animal and one high level animal).

#### Body Weight Changes

Individual weekly body weights and compound consumption are presented in Table No. 1. Mean body weights by group at initiation and at termination are presented below.

		Mean Body Weig	thts (kg.)	
		Group No.		
	_1	2	_3	4
Initial	2.5	2.4	2.2	2.1
Terminal	2.5	2.4	2.3	1.9

Animals in Groups No. 1, No. 2, and No. 3 generally maintained their initial weight or gained weight during the study. One animal at the low test level lost 10% of his initial weight. In Group No. 4, a general body weight decrease was noted with two animals losing 14% of their initial weight, one animal losing 10% of his initial weight, and one animal losing 5% of his initial weight.

## Clinical Studies

The results of the clinical studies for individual animals are presented in Tables No. 2 (hematology), No. 3 (biochemistry), and No. 4 (urine analyses).

The hematological data revealed slightly increased prothrombin time values at two weeks for one control monkey, three intermediate level monkeys, and four high level monkeys. The remaining hematological values were generally within normal limits and comparable to the control values.

Alterations in the biochemical data included occasional increases in fasting blood sugar values and serum glutamic-pyruvic transaminase values; but these increases were inconsistent, and no relation to compound administration was evident. A slight, dose-related decrease in alkaline phosphatase values was noted; however, these values remained within the normal range for laboratory monkeys.

The results of urine analyses were not remarkable.

#### Ophthalmoscopic Examination

Initial and terminal examination of the eyes of all monkeys revealed no compound-related ocular effects.

## Gross Pathology

At necropsy there were no gross organ or tissue alterations observed that could be attributed to the administration of the test material. Incidental changes which were noted at sacrifice included adhesions from lungs to pleura (one low level animal), lung mite lesions (one intermediate and one high level animal), enlarged spleen (one intermediate and one high level animal), rough surface of spleen (one intermediate level animal), and granular cut surface of spleen (one control and one intermediate level animal).

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## Organ Weights

Individual terminal body weights, organ weights, and organ/body weight ratios are presented in Table No. 5. Mean organ/body weight ratios by group are presented below.

	Organ		tio - Mean Value	es (%)
	<del></del>	Group		<del></del>
	_1_		3	4
Thyroid	0.016	0.015	0.016	0.018
Heart	0.441	0.426	0.415	0.438
Liver	2.739	2.183	2.269	2.472
Spleen	0.113	0.136	0.175	0.136
Kidneys	0.423	0.553	0.385	0.405
Adrenals	0.019	0.018	0.021	0.025
Testes	0.047	0.042	0.054	0.053
Prostate	0.011	0.014	0.013	0.014

With the exception of a high liver weight and ratio in one control monkey, all of the organ weight data were generally comparable among the control and test animals.

# Microscopic Pathology

Microscopic examination failed to reveal compound-related changes in the tissues examined. Incidential findings consisted of pituitary cysts in Monkey No. 534J (Group No. 1) and minimal lesions of encephalitis in Monkey No. 534J (Group No. 1) and Monkey No. 566J (Group No. 4). Granular, brown, birefringent pigment suggestive of lung mite infestation was noted in both control and treated animals.

Occasional foci of hepatocytic necrosis with nonsuppurative pericholangitis, occasional fcci of interstitial nephritis, nonsuppurative cystitis, and prostatitis were noted as spontaneous disease lesions.

As an incidental finding, the section of skeletal muscle from Monkey No. 531J (Group No. 4) revealed myositis with mononuclear inflammatory cells, muscle fiber regeneration, and fibroplasia. Sections of skeletal muscle from all other animals were not remarkable in appearance.

Level of activity of the thyroid gland and bone marrow, based on microscopic appearance, was comparable between control and treated animals. Appearance of all other tissues examined was essentially not remarkable and comparable between control and treated animals.

In conclusion, administration of the test compound (WR 2721) at levels of 8.3 mg/kg/day, 25 mg/kg/day, and 75 mg/kg/day for a 28-day period failed to cause microscopically demonstrable, compound-related changes in the tissues examined.

Detailed histologic findings in individual animals and an incidence table of histological alterations are appended to this report.

Submitted by

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Report Preparation: Novak Supervision: Thompson

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# EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

0 = negative

T = trace (±)

1 = slight (+)

2 = moderate (++)

3 = marked (+++)

4 = severe (++++)

TNTC = too numerous to count

Table No. 1 - Weekly body weights and compound consumption for male monkeys.

WR 2721 ORALLY BY INTUBATION DAILY FOR FOUR WEEKS

Wt. Change, kg.	5*	4	w	2	1	Initial	TIME INTERVAL Weeks
+0.2	2.6	2.5	2.5	2.5	2.4	2.4	MALE MONKEY NO. 530J WEIGHT kg.
+0.1	2.8	2.8	2.7	2.8	2.6	2.7	MALE MONKEY NO. 534J WEIGHT kg.
0	2.5	2.5	2.4	2.4	2.4	2.5	CONTROL MALE MONKEY NO. 573J WEIGHT kg.
-0.1	2.1	1.8	2.1	2.2	2.0	2.2	MONKEY NO. 581J WEIGHT

<sup>\*</sup> Vehicle was administered for three days in the fifth week.

Table No. 1 - Continued

WR 2721 ORALLY BY INTUBATION DAILY FOR FOUR WEEKS

Total Cpd. Adm., g.	Wt. Change, kg.	5*	4	w	2	₩	Initial	INTERVAL	TIME	
	<b>t0.1</b>	2.4	2.5	2.3	2.4	2.3	2.3	WEIGHT kg.	MONKEY	
0.59		0.06	0.13	0.14	0.13	0.13		g/week	MALE MONKEY NO. 529J	
	-0.3	2.5	2.6	2.6	2.5	2.5	2.8	WEIGHT kg.	MONKEY	
0.68		0.07	0.15	0.15	0.15	0.16		g/week	MALE MONKEY NO. 561J	8.3 MG/KG/DAY
	0	2.2	2.1	2.1	2.2	2.1	2.2	kg.	MONKEY	
0.55		0.05	0.12	0.13	0.12	0.13		g/week	MALE MONKEY NO. 572J	
	0	2.4	2.4	2.4	2.4	2.4	2.4	kg.	HONKEY	
0.62		0.06	0.14	0.14	0.14	0.14		g/week	MALE MONKEY NO. 575J	

<sup>\*</sup> Compound was administered for three days in the fifth week.

Table No. 1 - Continued

WR 2721 ORALLY BY INTUBATION DAILY FOR FOUR WEEKS

Total Cpd. Adm., g.	Wt. Change, kg.	5 <b>*</b>	4	w	2	1	Initial	INTERVAL	TIME	
	<del>+0.1</del>	2.2	2.1	2.1	2.2	2.1	2.1	WEIGHT kg.	MALE	
1.66		0.16	0.37	0.39	0.37	0.37		REIGHT COMPOUND kg. g/week	LE COL	
	<b>5.1</b>	2.2	2.1	2.1	2.1	2.1	2.1	WEIGHT kg.	Z.	
1.64		0.16	0.37	0.37	0.37	0.37		EIGHT COMPOUND kg. g/week	MALE	25 MG/KG/DAY
	to.1	2.3	2.4	2.2	2.3	2.1	2.2	WEIGHT kg.	X.	KG/DAY
1.73		0.18	0.39	0.40	0.37	0.39		MONKEY NO. 463J BIGHT COMPOUND kg. g/week	MALE	
	<b>5.1</b>	2.4	2.3	2.3	2.3	2.3	2.3	MEIGHT kg.	Z	
1.77		0.17	0.40	0.40	0.40	0.40		MONKEY NO. 571J  WEIGHT COMPOUND  kg. g/week	MALE	

 $<sup>\</sup>star$  Compound was administered for three days in the fifth week.

Table No. 1 - Continued

WR 2721 ORALLY BY INTUBATION DAILY FOR FOUR WEEKS

Total Cpd. Adm., g.	Wt. Change, kg.	<b>5</b> *	4	w	2	1	Initial	TIME INTERVAL Weeks
	-0.3	1.8	1.8	1.9	2.0	1.9	2.1	MONKEY WEIGHT
4.62		0.41	1.02	1.05	1.02	1.12		MALE MONKEY NO. 531J EIGHT COMPOUND kg. g/week
	-0.3	1.9	1.9	2.0	2.2	2.2	2.2	MALE MONKEY NO. WEIGHT CC kg.
4.97		0.44	1.05	1.16	1.16	1.16		MALE HONKEY NO. 560J EIGHT COMPOUND kg. g/week
	-0.2	1.8	1.7	1.7	1.8	1.7	2.0	G/DAY  MALE  MONKEY NO.  WEIGHT CO.  kg. 8
4.21		0.39	0.91	0.95	0.91	1.05		Y  MALE MONKEY NO. 565J  MEIGHT COMPOUND kg. g/week
	-0.1	2.1	2.1	2.0	2.1	2.1	2.2	MALE MONKEY NO.
4.93		0.48	1.05	1.12	1.12	1.16		MALE MONKEY NO. 566J EIGHT COMPOUND kg. g/week

<sup>\*</sup> Compound was administered for three days in the fifth week.

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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS

GROUP	1414	3 3 3 3 GROUP	GROUP	2222	GROUP		GROUP NUMBER
MEAN	531 J 560J 565J 566J	462J 463J 461J 571J	MEAN	529J 561J 572J 575J	MEAN	530J 534J 573J 581J	AN IMAL NUMBER
	3333	3333		3333		3333	×m×
39.5	41.0 40.0 40.0 37.0	43.0 42.0 41.0 39.0	40.8	43.0 40.0 40.0	42.3	43.0 43.0 43.0	#CT
13.8	14.6 14.6 13.5 12.3	14.6 15.0 14.2 13.2	14.2	14.6 13.7 14.2 14.2	14.7	15.0 14.6 15.0 14.2	н6в 6%
5.42	5.42 5.44 5.61 5.18	5.49 6.10 5.50 5.53	5.58	5.80 5.88 4.98	5.70	5. 65 5. 69 5. 89	RBC MILLS
13.1	12.5 10.5 14.3 14.9	14.6 14.1 16.1 13.8 14.7	16.9	16.1 11.3 30.5 9.7	16.3	22.7 12.9 11.5 17.9	WBC THS
	0000	0000		0000		0000	A L L K
	0000	0000		0000		0000	BAND
	17 16 54 20	28 18 51 44		27 30 31 19		34 13 34	DIFFER SEG %
	82 84 84 84 84 84	68 77 49 56		71 68 69 78		64 82 78	DIFFERENTIAL Seg Lymph % %
	0 - 00	0000		2000		0100	ONON
	o <b>-</b> 30	4 t/C C		-022		0 33 57 8	NISUB
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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS 2ND INITIAL

GROUP	444	GROUP	GROUP	2222	GROUP	<b></b>	GROUP NUMBER
MEAN	531J 560J 565J 566J	462J 463J 461J 571J MEAN	MEAN	529J 561J 572J 575J	MEAN	530J 534J 573J 581J	N A
	3333	3333		2223		3333	×m×
35.0	35.0 34.0 35.0 36.0	40.0 38.0 40.0 36.0	35.8	41.0 35.0 34.0 33.0	38.0	40.0 40.0 32.0 40.0	#C7
11.4	11.0 11.5 11.3 11.7	12.6 12.7 13.0 11.5	11.5	13.2 11.0 11.0 10.7	12.4	13.0 13.0 10.5 13.0	HGB 6%
5.15	4.91 5.07 5.35 5.27	5.32 5.42 5.56 5.24 5.39	5.18	5.89 5.29 4.76 4.76	5.40	5.72 5.75 4.60 5.53	RBC MILLS
12.3	11.5 11.3 9.8 16.5	12.5 9.4 7.6 15.3	15.7	17.0 13.8 19.2 12.8	17.6	19.2 14.7 16.4 19.9	WBC THS
	0000	0000		0000		0000	META -
	0 - 20	0000		0000		0000	BAND
	17 52 20 35	10 20 12		46 37 20 25		30 9 52 42	DIFFEI SEG %
	82 45 77 62	86 71 87 66		52 63 79		68 48 57	ERENTIAL LYMPH
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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS WEEK 2

			162		
GRAUP	4444	GROUP	SRUMA SRUMA	1 1 1 1 GR <i>OUP</i>	GROUP NUMBER
MEAN	531.1 560.1 565.1 566.1	461J 462J 463J 571J	529J 561J 575J 975J	530J 534J 573J 58IJ MEAN	ANIMAL
	2223	3253	2222	ZZZZ	× m ×
38.0	40.0 40.0 39.0 33.0	41.0 39.0 40.0 37.0 39.3	42.0 35.0 40.0 40.0	40.0 38.0 40.0 42.0	» CT
12.3	12.7 13.4 12.3 10.7	13.5 12.7 13.5 12.0	14.0 11.5 13.0 13.0	13.0 13.2 13.5	HGR <b>G</b> X
5.11	5.27 5.19 5.47 4.49	5.36 5.36 5.37	5.60 5.25 5.15 5.71	24. 69. 60. 86. 86. 5. 7. 86.	RBC MILLS
7.0	4.7 10.4 5.2 7.8	7.5 10.7 6.9 9.7	7.2 10.5 11.2 7.8 9.2	11.1 8.2 5.9 13.4	WRC THS
	0000	9999	3333	0000	META ATAM
	2000	0000	0000	0000	BAND %
	40 49 15 32	33 19 24 50	18 21 27	15 16 24 42	DIFFER
	55 45 45	73 73 48	81 79 68 84	79 78 62 57	IFFERENTIAL SEG LYMPH
	0 N W N	2001	၁ພ၁၁	0340	NONO
	0 N N W	0340	<b>200</b>	6 11 1	WISO3
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EAM	566.0 11	5650 =			HEAM		47.4.7	462J E		I-FVM					529J h	\$1EAL	2012			530J H		VIATHAT E	
36.5	34.0	38.0	37.0	37.0	39.3	35 35 31	40.0	43.0	39.0	39.0	50.0		מג מג	37.0	43.0	41.3	43.0		40.0	%1.0	Ж	нст	
12.2	11.0	12.7	12.3	12.7	13.1	11.8	3.4	] 4. R	12.4	12.9	17.1	1 0 0 H	1 ;	12.0	13.7	13.7	1.4.1	; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ;	) . ) .	13.4	£	HGR	E 7
4.87	4.35	5.40	4.76	4.97	5 • 33 33	5.12	5.09	5.94	5• <u>1</u> .8	5.44	5.53		л : 000	5.50	5.63	5.33	5.70	5.15	• • • •	5.07	HILLS	РКС	TABLE MO. 2 - IPDIVIDUAL HEBATOLOGICAL RHESUS BOMKEYS RECEIVING UR 272J EOR FOUR MEEK 4
7.3	6.2	7.4	10.5	5.1	14.7	15.7	14.4	16.5	10.3	10.1	:: 4	. x	) : 	12.4	.9 æ	10.1	15.0	7.7	χ. 5	9.3	SHI	идC	MO. 2 - II MOMKEYS REC MEEK
	Э	<b>-</b>	<b>၁</b>	0		Э	Э	С	0		Э	S	2	<b>)</b> ;	<b>-</b>		Э	)	0	0	• 7	V L3 H	IPDIV RECEIV FK 4
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	42	بر 0	37	62		56	S S	53 33	44		20	30	3	د د د د	36		19	بر در	<u>)</u> 4	% 30	:5	DIFFE	нЕ∺АТГ 272]
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TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS

13.9		MEAN	GROUP	
12.6	3	566J	4	
12.1	3	F595	4	
14.2	3	560J	4	
16.5	3	531ป	4	
12.4		MEAN	GROUP	
14.3	3	571J	w	
-	3	461 J	w	
12.2	3	463J	<b>ر</b> ى	
11.9	3	462J	w	
12.9		MEAN	GROUP	
13.6	3	575J	2	
2	Z	572J	2	
12.9	3	561 J	2	
13.0	3	529J	2	
13.4		MEAN	GROUP	
Ü	3	581J	~	
13.7	3	573J	<b>,_</b>	
13.2	3	534J		
w	3	530J	_	
SECONDS	×		NUMBER	
PROTHROMB IN	æ	ANIMAL	GROUP	

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS 2ND INITIAL

GROUP MEAN	4 565J M	560J		GROUP MEAN	571J		463J		GROUP MEAN	575J	572J	561J	2 529J M	GROUP MEAN		1 573J M		1 530J N	GROUP ANIMAL E
13.7	13.4	15.4	12.1	13.3	14.4	13.7	12.8	12.1	14.0	13	13	14	13.6	12.9	12	13.8	12	12	PR

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TABLE NO. 2 - INDIVIDUAL HEHATOLOGICAL VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR NEEKS NEEK 2

18.2	3 2 3	565J 566J MEAN	₹
17.5 18.6 17.9	<b>3 3</b>	MEAN 531J 560J	GROUP
17.6 18.4 15.9 18.1	SZZZ	461J 462J 463J 571J	ເມເນເນເນ
16.2		MEAN	GROUP
16.4 16.9 15.8 15.5	ZZZZ	529J 561J 572J 575J	N N N N
16.0		MEAN	GROUP
14.5 15.8 16.4 17.1	Z Z Z Z	530J 534J 573J 581J	فسز مينز فينز فينز
PROTHROMB IN SECONDS	$\times$ $\pi$ $\times$	AN IMAL NUMBER	GROUP NUMBER

nic justine

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HEM = SAMPLE HEMOLYZED

14.0		N C N	GROUP I	
12.7	₹	5661	4	
13.8	Z	565J	4	
14.6	7	560J	4	
14.7	2	531J	4	
14.8		MEAN	GR OUP	
16.2	三	571J	س	
14.8	Ξ	FE94	w	
13.2	Z	462J	'n	
14.8	Ξ	461J	ω	
13.4		MEAN	GROUP	
HFN	ĭ	575.	N	
12.8	Z	572J	N	
13.1	Ξ	561.1	N	
14.2	T	529J	N	
13.4		MEAN	GROUP	
13.5	Ξ	581 J	;	
17.8	Ξ	5731	<b></b>	
N.	=	534J	,	
14.6	3	530J	•••	
SECOMOS	×	PURRER	MUHRER	
PROTHROMS IN	TT 5	VELLAV	GROUP	
	•			

TABLE MO. 2 - IMDIVIDUAL HEMATOLOGICAL VALUES RHESUS MONKEYS RECEIVING MR 2721 FOR FOUR MEEKS WEEK 4

168

GROUP MEAN

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GROUP MEAN GROUP MEAN GROUP MEAN GROUP ANIMAL E NUMBER NUMBER X **(1) (1) (1) (1)** 565J M 560J M 463J M 461 J M 530J M 534J M 572J 575J 571J 573J 581J 531 J 461 J 462J 561 J 529J M 3 GLUCOSE 105.0 100.0 77.0 105.0 124.0 91.0 110.0 120.0 93.0 120.0 102.3 104.0 102.0 84.0 65.0 99.3 90.0 75.0 24.5 23.0 18.0 14.0 31.0 26.0 27.0 17.6 16.0 15.5 21.0 12.0 19.0 23.5 17.0 12.0 16.0 8.0 31.0 41.0 37.5 39.0 39.0 32.5 34.0 37.5 44.0 37.5 42.5 34.0 64.5 32.9 29.0 31.0 34.0 37.5 SGPT R-F. ALK.PHOS 37.9 56.0 60.4 33.8 60.0 42.9 77.6 80 52.0 85.6 43.2 72.0 42.5 92.0 50.9 60.1 63.2 74.4 BILIRUBIN TOTAL MG% 0.20 0.40 0.49 0.20 0.45 0.21 0.30 0.40 0.35 0.30 0.27 0.28 0.40 0.29 0.20 BILIRUBIN DIRECT 0.06 0.04 0.04 0.04 0.06 0.05 0.05 0.08 0.04 0.08 0.06 0.13 0.06 0.02 0.06 0.06 0.06 3 3 3 3

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS

1ST INITIAL

169

GROUP MEAN

62.3

0.02

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GROUP ANIMAL E NUMBER NUMBER X GROUP MEAN GROUP MEAN GROUP MEAN 531 J M 560J M 572J 575J 530J 534J 461J 571J 573J 581J 565J M 463J M 462J M 561J M 529J M 3 GLUCOSE 95.0 105.0 100.0 101.0 110.0 104.0 105.0 110.0 118.0 95.0 84.0 96.0 81.0 70.0 94.8 98.0 20.5 20.0 15.0 25.5 16.0 16.5 19.1 13.8 11.0 12.0 16.5 14.5 14.0 16.0 16.0 MGX MGX 17.3 57.0 34.0 SGPT 31.0 36.0 23.0 32.5 26.0 29.0 32.5 31.0 34.0 37.0 26.0 31.0 31.0 27.6 34.0 2ND INITIAL ALK.PHOS K-A.UNITS 64.8 60.5 55.6 57.6 56.8 75.2 98.8 94.8 47.1 74.4 85.6 42.2 77.2 89.6 86.8 78.4 75.2 72.0 76.7 BILIRUBIN TOTAL 0.20  $0.30 \\ 0.19$ 0.25 0.21 0.20 0.30 0.22 0.21 0.19 0.20 0.25 0.30 0.19 0.25 BILIRUBIN DIRECT 0.02 0.02 0.02 0.04 0.04 0.02 0.04 0.06 0.04 0.03 0.02 0.02 0.04 0.04 0.04

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS

TARLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MUNKEYS RECEIVING WR 2721 FOR FUUK WEEKS
24 HOURS

GROUP	444	3 3 3 3 3 0 0 0 0 0	2 2 2 2 5 6 8 9 9	1 1 1 1 680UP	GRAUP NUMBER
MEAN	531J 560J 565J 566J	461J 462J 463J 571J	529J 561J 572J 575J	530J 534J 573J 581J MEAN	AN IMAL NUMBER
	SSSS	2233	3223	2223	×m ×
17.0	16.0 23.0 13.0 16.0	20.0 16.0 18.0 41.0	19.0 22.0 20.0 25.0 21.5	18.0 23.0 20.0 20.0	BUN MG%
39.3	42.5 32.5 41.0 41.0	75.0 39.0 39.0 34.0 46.8	39.0 39.0 37.5 34.0	41.0 41.0 50.0 28.0 40.0	SGPT R-F.
0.22	0.22 0.25 0.18 0.22	0.25 0.25 0.22 0.27 0.27	0.22 0.29 0.16 0.16 0.21	0.22 0.20 0.25 0.25 0.25	BILIRUBIN TOTAL MG%

TARLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
48 HOURS

GROUP	4	4	4	4	GROUP	ىن	ىن	w	w	GROUP	2	2	~	2	GROUP	<b></b>		<b></b> -	-	NUMBER	GROUP	
MEAN	566J	565J	560J	531J	MEAN	571J	463J	462J	461J	MEAN	-	-1	561 J	2	MEAN	581J	573J	534J	530J	NUMBER	ANIMAL	
	3	3.	Z	I		I.	2	3	<u> </u>		3	I	I	3		3	3.	3	Z	×	æ	S
12.6	10.5	12.0	14.0	14.0	17.5	20.0	17.0	6	17.0	15.5	18.0	16.0	14.0	14.0	14.5	12.0	15.0		17.0	₹G%	RUN	
36.5	34.0	39.0	34.0	39.0	39.9	34.0	36.0	37.5	52.0	33.6	37.5	34.0	34.0	29.0	32.5	31.0	29.0	32.5	37.5	R-F.	SGPT	
0.20	0.23	0.17	0.21	0.19	0.31	0.40	0.25	0.23	0.34	0.26	0.21	0.28	0.25	0.30	0.32	0.25	0.34	0.42	0.28	×95.	TOTAL	BILIRUBIN

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR MEEKS
72 HOURS

GKOUP	222	Р	w w w	GROUP	N N N N	7		GROUP NUMBER
MEAN	531J 560J 565J 566J	571J MEAN	461 J 462 J 463 J	MEAN	561J 572J 575J	MEAN	530J 534J 573J 581J	AN IMAL
	Z Z Z Z	3	<b>Z Z Z</b>		3213	3	3 2 2 2	$\times$ m $\otimes$
16.0	16.0 17.0 14.0 17.0	20.0	20.0 20.0 17.0	18.3	14.0 16.0 22.0 21.0	5	22.0 12.0 12.0 15.0	BUN MG%
37.5	42.5 36.0 37.5 34.0	39.0 39.6	46.0 37.5 36.0	36.6	37.5 34.0 36.0	38.4	41.0 37.5 39.0 36.0	SGPT
0.25	0.25 0.22 0.27 0.27	0.29	0.20 0.22 0.29	0.31	0.31	0.27	0.25 0.20 0.27 0.36	BILIRUBIN TOTAL MG%

TABLE NO. 3 - IMDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MOMKEYS RECEIVING WR 2721 FOR FOUR MEEKS WEEK 2

											17.	2									
GREHIP	4	4	4	4	GROUP	w	Ų	ىر	ω	GROUP	·		N	N	GRAUP	<b>,</b>		<b>,_</b>	<b>,</b>	NUMBER	
MEAN	566J	565.1	560.1	531ป	MEAN	571J	463J	462J	461J	MEAN	575J	572J	561J	529.1	MEAN	581J	5 <b>7</b> 3J	534J	530J	NUMBER	2
				Z		Ξ			3				⋾					Z		× :	n o
82.0	76.0	85.0	0.68	78.0	83.5	79.0	93.0	76.0	86.0	89.0	82.0	88.0	84.0	102.0	80.3	81.0	50.0	85.0	95.0	MG%	el licuse
14.9	13.0	11.5	18.0	17.0	20.5	35.0	16.0	14.0	17.0	17.0	15.0	16.0	19.5	17.5	15.9	14.0	11.5	20.5	17.5	мся	B
3 B . B	37.5	37.5	39.0	41.0	40.5	34.0	39.0	48.0	41.0	39.5	37.5	39.0	39.0	42.5	37.5	34.0	37.5	37.5	41.0	R-F.	269 T
41.8	31.5	48.1	57.6	30.0	44.7	50.0	41.0	42.6	45.0	50.3	39.0	44.1	41.7	76.4	60.8	50.0	45.0	74.4	73.6	K-A.UMITS	A1 K . PHOS
0.27	0.20	0.28	0.29	0.30	0.26	0.20	0.40	0.20	0.24	0.29	0.25	0.30	0.23	0.38	0.31	0.25	22.0	0.26	0.51	MG%	BILIRUBIN
0.02	0.02	0.02	0.0%	0.02	0.04	0.02	0.04	0.06	0.04	0.04	0.04	0.04	0.02	0.06	0.03	20.0	0.04	0.00	0.06	MG%	BILIRUBIN

TABLE MO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES BHESHS BONKEYS RECEIVING MR 2721 FOR FOUR MEEKS

											/	7	4	,							
dinasa	.5	4	4	>	GRAHP	'بر	در	ىر	ىر	ekunb i	<b>&gt;</b>		. 7	2	GRUUP		_	<b>,_</b>	; <del></del>	THUMBER	GROUP
PERM	566.1	565J	560J	531J	PEAN	571.1	1,531	462.1	461J	MEAN	575J	572J	561J	529.1	MEAN	581J	573ป	524J	530J	MHMRFR	VMIHVE
	K	Ţ.;	3	=		77		=	Ξ		Ξ	Z	=	7.*		7.7.	<u> Z</u>	3	7.7	×	TIS
8.Cd	30.0	0.1s	30.0 0	90.0	124.3	80.0	145.0	31.0	191.0	105.0	125.0	101.0	95.0	99.0	104.0	120.0	90.0	95.0	0.111	X UN	9Encose
15.1	13.5	13.0	15.0	19.0	22.6	31.0	16.0	25.0	18.5	17.1	10.0	13.5	18.0	រួន.០	16.8	18.0	15.0	11.0	23.0	% ₩0%	BIN
%O.9	46.0	37.5	37.5	42.5	35.5	28.0	36.0	39.0	39.0	37.9	37.5	34.n	39.0	41.0	36.6	39.0	37.5	36.0	3/1.0	R-F.	SapT
32.9	28.8	45.0	33.7	24.0	37.6	47.8	26.5	41.1	35.1	48.8	36.5	37.0	33.0	88.8	49.1	37.9	37.9	46.1	74.4	K-A.UMITS	VEK • beins
0.22	0.19	0.19	0.19	0.30	0.21	0.15	0.21	0.29	0.20	0.20	0.21	0.19	0.20	0.20	0.30	0.40	0.20	0.29	0.30	×9W	BILIRUBIA TOTAL
0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.06	0.02	0.04	0.05	0.04	0.06	0.04	0.04	0.05	0.06	0.06	0.06	0.02	<b>В</b>	BILIRUBIM DIRECT

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS

GROUP MEAN	4 566J	4 5651		GROUP MEAN		3 46ไป	3 462J	GROUP MEAN	2 5753	572	561		GROUP MEAN	Un	US:	1 534J	<b>U</b> T	NUMBER NUMBER	GROUP ANIMAL	
	3 :	3 3	3		3	<b>3</b> 3	2 2		3	3	3	3		3	3	3	3	×	ιπ	S
8.02	7.85	7.83	7.70	8.01	8.05	7.50	7.80	7.58	7.50	7.90	7.80	7.10	7.93	7.90	7.50	8.00	8.30	G#	PROTEIN	TOTAL
3.20	3.11			2.61	3.10	3.20	4.00	3.15	3.09	3.51	3.10	2.90	3.39	3.56	3.49	3.50	2.99	G¥.	AL BUM IN	TOTAL

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS 2ND INITIAL

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING HR 2721 FOR FOUR WEEKS WEEK 2

GROUP	4 4	44	GRAUP	ωι	ນ ເປ	w	GRAUP	2	2	2	2	GROUP	-	<b>,</b> —	-	1	GR OUP NUMBER
MEAN	565J	531J 560J	MEAN	571J	462J 463 J	461J	MEAN	75	572J	61	29	MEAN	581J	573J	534J	530J	ANIMAL
	I Z	<u> </u>		I 3	Z	Ξ		Ξ	Ξ	3	3		3	Z.	3	3	$\times$ m $\sim$
7.37	7.45 7.11	7.20 7.71	7.38	7.49	6.75 7.60	7.59	7.28	7.30	8.11	7.00	6.70	7.47	7.44	7.18	7.34	7.90	TOTAL PROTEIN G%
2.84	2.90 2.28	3.00 3.16	2.90	3.10	2.51	2.79	2.80	2.78	3.46	2.40	2.55	3.26	3.27		•	3 • 35	TOTAL ALBUMIN G%

TARLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING MR 2721 FOR FOUR MEPKS
PREK 4

GRIUP +	4	4	4	4	GROUP	لد	ند (	ı vı	ı w	CKUUP	2	) \	) N	v <b>~</b> ;	GRAUP				·	MUTBER	GRUND	
le E Λ N	566J M		560J N	531J H	МЕАН	571.J H			461J N	MEAN	575J M		561J F	529J N	MEAN			534J 1		NUMBER	VMILIVE	
7.35	7.35				7.30			7.75		6.98			7.15		7.68	N 7.85			P 7.40		F PROTEIN	STOTAL
2_89	2.55	2.95	3.00	3.05	2.73	3.00	2.55	2.80	2.55	2.80	2.60	3.15	2.65	2.80	3.16	3.20	3.40	3.05	ર 00	£25	WI SHEET	IVIOI

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS 1ST INITIAL

GROUP I	4444	GROUP	ເມເມເມ	GROUP	2222	GROUP		GR OUP NUMBER
MEAN	531 J 560 J 565 J 566 J	MEAN	462J 463J 461J 571J	MEAN	529J 561J 572J 575J	MEAN	530J 534J 573J 581J	ANIMAL NUMBER
	3 2 3 3		3333		3333		3333	×mv
1.00	0.80 1.20 1.10 0.90	1.15	1.00 1.30 1.20 1.10	1.08	1.30 1.20 0.80 1.00	1.20	0.90 1.20 1.30 1.40	SERUM CREAT. MG%
0.72	0.79 0.75 0.68 0.66	0.85	1.10 0.91 0.74 0.63	0.71	0.69 0.66 0.80 0.70	0.76	0.56 0.78 0.87 0.82	A/G RATIO

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS 2ND INITIAL

GROUP MEAN	4444	GROUP MEAN	wwww 444r	GROUP MEAN	N N N N	GROUP MEAN	<b></b>	GROUP ANI
	31 J 60J 66J		462J 463J 461J 571J		29J 61J 72J 75J	_	30J 34J 73J 81J	ANIMAL NUMBER
	3333		3333		3333		3333	× m ∨
1.15	1.00 1.40 1.10 1.10	1.30	1.00 1.20 1.40 1.60	1.00	0.90 1.00 0.80 1.30	1.08	1.30 0.80 1.10 1.10	SERUM CREAT. MGX
0.62	0.59 0.52 0.66 0.68	0.71	0.78 0.83 0.64 0.59	0.58	0.68 0.50 0.62 0.53	0.55	0.56 0.65 0.49 0.50	A/G RATIO

TABLE NO. 3 - INDIVIDUAL BLOWD CHEBISTRY VALUES RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS

24 HOURS

444	GROUP	ພູພູພູພູ	GROUP	N N N N	GROUP	سر سر سرسم	GR OUP NUMBER
531J 560J 565J 566J	MEAN	461J 462J 463J 571J	MEAN	529J 561J 572J 575J	MEAN	530J 534J 573J 581J	ANIMAL
REEE		2 2 2 2		2323		2233	×mv
1.30 1.20 1.10	1.25	1.20 1.30 1.30 1.20	1.20	1.20 1.30 1.20 1.10	1.13	1.30 1.10 1.00	CREAT.

GROUP MEAN

1.23

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING MR 2721 FOR FOUR WEEKS

48 HOURS

444	GROUP	6R.OUP 3 3	N N N N	1 1 1 1 1 1 1 1	GR DUP NUMBER
531J 565J 565J 565J	463J 571J MEAN	M E A	529J 561J 572J 575J	530J 534J 573J 581J	ANIMAL R NUMBER
M 1.20 M 1.20 M 1.00 M 1.30	M 1.2	مسر مسر • • •	0000	M 1.10 M 1.00 M 1.00 M 1.00	S SERUM E CREAT X MG%
20 20 00 30	သော ဝီဝီ	10	0000	10 00 00 00 00	•, -

GROUP MEAN

1.18

TABLE MO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING MR 2721 FOR FOUR VEEKS

**72 HOURS** 

GROUP 2 2 2 2 2 3 3 3 3 GROUP 4 4 4		GROUP NUMBER
81J 75J 75J 75J 75J 75J 75J 75J 75J 75J 75	530J M 534J M 573J M	ANIMAL E
1.25 1.30 1.30 1.30 1.20 1.20 1.20 1.20 1.20 1.20 1.20 1.2	1.30	SERUM CREAT. NG%

GROUP MEAN

1.20

TARLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING MR 2721 FOR FOUR MEEKS WEEK 2

GRAUP H	444	GROUP M	ພພພພຸ	GROUP M	N NN N	GROUP M	معر میں میں میں	GROUP I
MEVN	531J M 560J M 565J M 566J N	MEAN	461J M 462J M <b>463</b> J M 571J M	MEAN	529J M 561J M 572J M 575J M	MEAN	530J M 534J M 573J M 581J M	ANIMAL E
1.25	1.20 1.30 1.10 1.40	0.98	1.00 1.00 1.10 0.80	1.23	1.00 1.30 1.40 1.20	1.08	1.10 1.10 1.20 0.90	SERUM CREAT. MGZ
0.63	0.71 0.69 0.64 0.47	0.59	0.58 0.59 0.46 0.71	0.62	0.61 0.52 0.74 0.62	0.75	0.74 0.79 0.70 0.78	A/G RATIO

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About 1 March

TARLE NO. 3 - INDIVIOUAL BLOWN CHEHISTRY VALUES RHESUS MONKEYS RECEIVING MR 2721 FOR FUNK OFFEKS

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GROUP HEAD	4 560J M 4 566J M 4 566J M	3 461J M 3 462J M 3 463J M 3 571J M GROHP MFAN	2 529J R 2 561J N 2 572J R 2 575J R	RROUP ANTEACH NUMBER NUMBER NUMBER NUMBER X  1 530J H 1 534J H 1 573J M 1 581J M GROUP MEAN	•
1.08	1.10 1.00 1.00	1.20 1.30 1.40	1.00 1.10 1.30 1.20	1.00 1.00 1.00 1.20 1.20	SERIM
0.65	0.72 0.70 0.66 0.53	0.55 0.57 0.57 0.70	0.74 0.59 0.73 0.63 0.63	0.68 0.64 0.80 0.69	A/G RATIO

TABLE NO. 4 - URINE ANALYSIS
RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
1ST INITIAL

		186		
4444	ىن ئىن بىن	~~~		GROUP NUMBER
531 J 560 J 565 J 566 J	462J 463J 461 J 571 J	529 J 561 J 572 J 575 J	530J 534J 573J 581J	ANI MAL NUMBER
3333	3333	3333	3333	×mv
6767	8775	7070	0000	I T
1.017 1.027 1.025 1.010	1.014 1.023 1.011 1.008	1.029 1.015 1.012 1.032	1.024 1.017 1.031 1.031	SP.GR.
0000	0000	0000	0000	SU- GAR
0	00 - 0	-00 <del>-</del>	0 - 7 -	PRO-
0000	0000	0008	0010	BILI- RUBIN
0000	0000	0000	0000	0CC BL0
8 29 25 110	29 6 35	13 48 22 22	35 7 43 16	<b>V</b> 0L•
4-5	4 5	1 3	1-3	RBC
2-3 2-4	0-2 2-3 1-3	1-3	1-2 4-6 1-3	W BC
3-4	3-5	0-1 0-1 0-2	0-1	I CROSCI EP I TH
MUCH MUCH MUCH	MUCH MUCH MUCH	MUCH LITTLE MUCH	MUCH MUCH MUCH	DPIC FINDINGSAMORPH CRYS BACT SPERM
TI THE		77 TO	TI EN W	NDI NG CR YS
TI CE	W W W W W W W W W W W W W W W W W W W	MANY WY	THE HE	BACT
•				SPERM

TABLE NO. 4 - URINE ANALYSIS
RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS
2ND INITIAL

		187		
444	ري دي يي	2222	مبر مبر مبر	GROUP NUMBER
531 ) 560J 565J 566J	462J 463J 461J 571J	529 J 561 J 572 J 575 J	530J 534J 573J 581J	AN I MAL
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TABLE NO. 4 - URINE ANALYSIS RHESUS MONKEYS RECEIVING WR 2721 FOR FOUR WEEKS WEEK 2

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TABLE NO. 5 - TERRITORY REPORTS, DEGREE RETGHTS, AND DEGREE/ROLY RETGHT CATIOS

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# TABLE NO. 5 - CONTINUED

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# HISTOPATHOLOGICAL EVALUATION OF MALE RHESUS MONKEYS SACRIFICED AT TERMINATION

## GROUP NO. 1 Male Monkey No. 530J

Monkey No. 530J
MICROSCOPIC
Most follicles moderate to large in size and
lined by flattened cuobidal epithelium.
Activity slight.
Slight vacuolation of cells in zona fasciculata.
Slight artifactual separation of fibers in the
substantia propria of the cornea.
Artifactual distortion of the lens with formation
of small open spaces which contained granular
eosinophilic-staining material, representing
artifactual distortion at the time of fixation
and processing.
Numerous small accumulations of phagocytic cells
surrounding small blood vessels and air passages
These cells contained brownish black, birefringen
crystalline material, suggestive of mite pigment
in appearance.
Otherwise, not remarkable.

#### Liver:

No alterations observed.

Moderate vacuolation of hepatocytes throughout the section.

Minimal focal accumulations of mononuclear inflammatory cells in the liver parenchyma.

## GROUP NO. 1 Male Monkey No. 530J (Continued)

GROSS

MICROSCOPIC

Testis:

No alterations observed.

Seminiferous tubules small in size; and most

contained only Sertoli cells and spermatogonia

with occasional primary spermatocytes.

Appearance typical of immature testicular tissue.

Prostate:

No alterations observed.

Most of the acinar structures small in size with

the appearance of inactive prostate tissue.

Otherwise, not remarkable.

Bone Marrow:

No alterations observed.

Large numbers of maturing elements of both

erythroid and myeloid series.

Slight numbers of megakaryocytes.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, spleen, kidney, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, nerve/muscle, and rib.

#### GROUP NO. 1 Male Monkey No. 534J

**GROSS** 

MICROSCOPIC

Brain:

No alterations observed.

Several small vessels in the cerebrum surrounded by accumulations of mononuclear inflammatory cells, constituting perivascular cuffing.

There was no evidence of gliosis or neuronal degeneration.

Pituitary:

No alterations observed.

Small, fluid-filled cyst in the pars anterior.

Thyroid:

No alterations observed.

Most follicles moderate to large in size and
lined by slightly flattened cuboidal epithelium.
Activity slight.

Adrenal:

No alterations observed.

Slight vacuolation of the zona fasciculata.

Eye:

No alterations observed.

Artifactual separation of the substantia propria of the cornea.

Lung:

No alterations observed.

Slight amount of brownish, granular, birefringent pigment surrounding small blood vessels, suggestive in appearance of lung mite pigment.

Otherwise, not remarkable.

## GROUP NO. 1 Male Monkey No. 534J (Continued)

**GROSS** 

MICROSCOPIC

Spleen:

Appeared granular, on cut

surface.

Lymphoid hyperplasia characterized by increased numbers of small lymphocytes at the periphery of lymphoid follicles and increased cellularity in the parenchyma of the spleen.

Liver:

No alterations observed.

Moderate vacuolation of hepatocytes throughout

the section.

Small focal accumulations of mononuclear

inflammatory cells.

Kidney:

No alterations observed.

Minimal incidence of small focal accumulations of mononuclear inflammatory cells in the cortex.

Urinary Bladder:

No alterations observed.

Small perivascular accumulations of mononuclear inflammatory cells in the submucosal tissue.

Testis:

No alterations observed.

Appearance typical of immature testicular tissue with Sertoli cells, spermatogonia, and

primary spermatocytes in seminiferous tubules; however, spermatids and maturing spermatozoa

not evident.

Bone Marrow:

No alterations observed.

Large numbers of maturing elements of both

erythroid and myeloid series.

Slight numbers of megakaryocytes.

## GROUP NO. 1 Male Monkey No. 534J (Continued)

GROSS

MICROSCOPIC

The following organs were not altered grossly or microscopically: spinal cord, heart, gallbladder, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, prostate, nerve/muscle, and rib.

## GROUP NO. 1 Male Monkey No. 573J

**GROSS** MICROSCOPIC Thyroid: No alterations observed. Most follicles moderate to large in size and lined by flattened cuboidal epithelium. Activity slight. Adrenal: No alterations observed. Slight to moderate vacuolation of zona fasciculata Eye: No alterations observed. Slight artifactual distortion of the cornea. Slight artifactual distortion of the lens. Heart: No alterations observed. Single small focus of nonsuppurative myocarditis with focal accumulations of mononuclear inflammatory cells. Lung: No alterations observed. Small amount of brownish, granular, birefringent pigment surrounding small blood vessels, suggestive of mite pigment in appearance. Several small focal areas of lymphoreticular cell proliferation. Spleen: No alterations observed. Slight lymphoid hyperplasia. Slight increased numbers of lymphocytes in lymphoid follicles and interfollicular tissue.

the section.

Moderate vacuolation of hepatocytes throughout

Liver:

No alterations observed.

# GROUP NO. 1 Male Monkey No. 573J (Continued)

GROSS

MICROSCOPIC

Urinary Bladder:

No alterations observed.

Minimal focal cystitis with focal accumulations

of mononuclear inflammatory cells some of

which were in the mucosa.

Testis:

No alterations observed.

Microscopic appearance typical of immatuz

testicular tissue.

Bone Marrow:

No alterations observed.

Moderately large numbers of maturing elem. . of

both erythroid and myeloid series.

Slight numbers of megakaryocytes.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, gallbladder, kidney, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, prostate, nerve/muscle, and rib.

## GROUP NO. 1 Male Monkey No. 581J

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Most follicles moderate to large in size and  $% \left( 1\right) =\left( 1\right) \left( 1\right)$ 

lined by flattened cuboidal epithelium.

Activity slight.

Adrenal:

No alterations observed.

Slight to moderate vacuolation of the zona

fasciculata.

Small mineralized area at the corticomedullary

junction.

Eye:

No alterations observed.

Slight artifactual distortion of the cornea and

posterior portion of the lens.

Lung:

No alterations observed.

Slight amount of brownish, granular birefringent

pigment surrounding small blood vessels and

occasional focal accumulation of foamy

macrophages.

Otherwise, not remarkable.

Liver:

No alterations observed.

Slight to moderate vacuolation of hepatocytes

throughout the section.

Focal areas of nonsuppurative hepatitis

characterized by focal accumulations of

mononuclear inflammatory cells and coagulation

necrosis of hepatocytes, distribution of these

lesions, primarily, in the subcapsular region;

although, occasional foci noted throughout the

section.

# GROUP NO. 1 Male Monkey No. 581J (Continued)

GROSS MICROSCOPIC

Kidney:

No alterations observed.

Focal interstitial nephritis characterized by accumulations of mononuclear inflammatory cells, necrosis of tubule epithelium, and regeneration of tubule epithelium.

Testis:

No alterations observed.

Histologic picture typical of immature testicular tissue.

Bone Marrow:

No alterations observed.

Large numbers of maturing elements of both erythroid and myeloid series.

Slight numbers of megakaryocytes.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, spleen, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, prostate, nerve/muscle, and rib.

## GROUP NO. 2 Male Monkey No. 529J

GROSS \_\_\_\_

\_\_\_\_

MICROSCOPIC

Liver:

No alterations observed.

Slight vacuolation of hepatocytes throughout

the section, most pronounced in centrilobular

region.

Kidney:

No alterations observed.

Minimal interstitial nephritis with focal

accumulations of mononuclear inflammatory cells.

GROUP NO. 2 Male Monkey No. 561J

**CROSS** 

MICROSCOPIC

Liver:

No alterations observed.

Slight vacuolation of hepatocytes throughout

the section.

The following organ was not altered grossly or microscopically: kidney.

## GROUP NO. 2 Male Monkey No. 572J

GROSS \_\_\_\_\_

MICROSCOPIC

Liver:

No alterations observed.

Slight to moderate vacuolation of hepatocytes

throughout the section.

Minimal nonsuppurative pericholangitis.

Slight degree of hepatitis characterized by

focal accumulations of neutrophils, primarily,

in the subcapsular region.

Kidney:

No alterations observed.

Minimal interstitial nephritis characterized by

focal accumulations of mononuclear inflammatory

cells in the renal medulla.

GROUP NO. 2 Male Monkey No. 575J

**GROSS** 

MICROSCOPIC

Liver:

No alterations observed.

Slight vacuolation of hepatocytes in the

centrilobular regions.

Kidney:

No alterations observed.

Minimal interstitial nephritis with focal

accumulations of mononuclear inflammatory

cells in the renal medulla.

## GROUP NO. 3 Male Monkey No. 461J

**GROSS** 

MICROSCOPIC

Liver:

No alterations observed.

Moderate vacuolation of hepatocytes throughout the section.

Occasional small focus of nonsuppurative
hepatitis characterized by focal accumulations
of mononuclear inflammatory cells and necrotic
hepatocytes.

Vasculitis affecting the branches of the hepatic arteries in the portal triads with infiltrations of mononuclear inflammatory cells into the vessel walls and in the perivascular tissue.

Slight nonsuppurative pericholangitis.

#### Kidney:

No alterations observed.

Slight interstitial nephritis characterized by focal accumulations of mononuclear inflammatory cells, regenerative tubule epithelium, and perivascular accumulations of mononuclear cells.

Slight amount of eosinophilic-staining, granular material in Bowman's space of numerous glomeruli representing protein leakage.

In several of the areas of inflammation, eosinophilic-staining intranuclear inclusion

bodies noted.

GROUP NO. 3 Male Monkey No. 462J

lesions.

Liver:

No alterations observed.

Slight to moderate vacuolation of hepatocytes,
most pronounced in centrilobular region.

Slight nonsuppurative pericholangitis.

Kidney:

No alterations observed.

Minimal interstitial nephritis characterized by
focal accumulations of mononuclear inflammatory
cells in the cortex and medullla.

Unusual Lesion:
Lung - A few lung mite

Section not examined microscopically.

### GROUP NO. 3 Male Monkey No. 463J

**GROSS** 

MICROSCOPIC

Liver:

No altera . s observed.

Slight vacuolation of hepatocytes, predominantly

in the centrilobular region.

The following organ was not altered grossly or microscopically: kidney.

## GROUP NO. 3 Male Monkey No. 571J

**GROSS** 

MICROSCOPIC

Liver:

No alterations observed.

Slight nonsuppurative pericholangitis.

Slight vacuolation of hepatocytes throughout the

section, predominantly in the centrilobular

region.

Kidney:

No alterations observed.

Minimal interstitial nephritis with focal

accumulations of mononuclear inflammatory

cells.

Unusual Lesion:

Spleen - Slightly enlarged

with rough surface.

Cut surface appeared slightly

granular.

Section not examined microscopically.

## GROUP NO. 4 Male Monkey No. 531J

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Large peripheral follicles lined by flattened

epithelium.

Follicles in center of gland, moderate in size

and lined by slightly flattened cuboidal

epithelium.

Activity slight to moderate.

Adrenal:

No alterations observed.

Slight vacuolation of cells in zona fasciculata.

A small concentric focus of mineralization

at the corticomedullary junction.

Eye:

No alterations observed.

Slight artifactual distortion of the cornea and

lens.

Lung:

No alterations observed.

Occasional small focal area of lymphoreticular

cell proliferation.

One of the small muscular arteries in the

peribronchial region revealed intimal

thickening.

Liver:

No alterations observed.

Slight vacuolation of hepatocytes throughout

the section, especially in the centrilobular

region.

## GROUP NO. 4 Male Monkey No. 531J (Continued)

**GROSS** 

MICROSCOPIC

Testis:

No alterations observed.

Seminiferous tubules composed of Sertoli cells,

spermatogonia, occasional primary spermatocytes.

Spermatids and maturing spermatozoa were

not evident.

Appearance typical of immature testicular tissue.

Prostate:

No alterations observed.

Single small focus of reticuloendothelial cell proliferation, constituting a small focal area of nonsuppurative prostatitis.

Nerve/Muscle:

No alterations observed.

Nerve tissue essentially normal in appearance; however, a focal area of nonsuppurative myositis characterized by slight numbers of mononuclear inflammatory cells, hemosiderin-laden macrophages, occasional necrotic muscle fibers, and marked proliferation of sarcolemmal nuclei in an attempt at muscle fiber regeneration Fibroplasia evident.

Bone Marrow:

No alterations observed.

Large numbers of maturing elements of both erythroid and myeloid series.

Slight numbers of megakaryocytes.

# GROUP NO. 4 Male Monkey No. 531J (Continued)

GROSS

MICROSCOPIC

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, spleen, kidney, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, and rib.

## GROUP NO. 4 Male Monkey No. 560J

**GROSS** MICROSCOPIC Thyroid: Most follicles moderate to large in size and No alterations observed. lined by flattened cuboidal epithelium. Activity slight. Adrenal: No alterations observed. Slight to moderate vacuolation of the zona fasciculata. Concentric foci of mineralization at the corticomedullary junction. Small focus of adipose tissue in the medulla. Eve: Slight artifactual distortion of the cornea. No alterations observed. Severe artifactual distortion of the lens. Lung: No alterations observed. Slight amount of brownish, granular, birefringent pigment, suggestive of lung mite pigment. Focal area of artifactual collapse of the lung parenchyma. Liver: No alterations observed. Slight to moderate vacuolation of hepatocytes, most pronounced in the centrilobular region. Testis: No alterations observed. Appearance typical of immature testicular tissue. Prostate: Section not available for examination. No alterations observed.

# GROUP NO. 4 Male Monkey No. 560J (Continued)

**GROSS** 

MICROSCOPIC

Bone Marrow:

No alterations observed.

Moderately large numbers of maturing elements of both erythroid and myeloid series.

Slight numbers of megakaryocytes.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, spleen, kidney, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, nerve/muscle, and rib.

### GROUP NO. 4 Male Monkey No. 565J

GROSS

Thyroid:

No alterations observed.

Follicles moderate to large in size and lined

MICROSCOPIC

by flattened cuboidal epithelium.

Activity slight.

Adrenal:

No alterations observed.

Slight to moderate vacuolation of zona fasciculata

Eye:

No alterations observed.

Slight artifactual distortion of the cornea and

lens.

Lung:

No alterations observed.

Small area of artifactual collapse.

Occasional small focus of lymphoreticular cell

proliferation.

Slight amount of brownish, granular, birefringent

pigment, suggestive of lung mite infestation.

Spleen:

Appeared enlarged.

Proliferation of lymphoreticular elements with increased prominence of germinal centers and

increased numbers of reticulum cells in the

interfollicular tissue.

Liver:

No alterations observed.

Moderate vacuolation of hepatocytes throughout

the section, most pronounced in centrilobular

region.

Occasional focus of necrotic hepatocytes

surrounded by mononuclear inflammatory cells.

Slight nonsuppurative pericholangitis.

# GROUP NO. 4 Male Monkey No. 565J (Continued)

GROSS MICROSCOPIC

Kidney:

No alterations observed.

Minimal interstitial nephritis with focal

accumulations of mononuclear inflammatory cells.

Testis:

No alterations observed.

Appearance typical of immature testicular tissue.

Bone Marrow:

No alterations observed.

Large numbers of maturing elements of both

erythroid and myeloid series.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, prostate, nerve/muscle, and rib.

# GROUP NO. 4 Male Monkey No. 566J

GROSS Hale Homey No. 3003

MICROSCOPIC

Brain:

No alterations observed.

Small focal accumulations of glial cells with perivascular accumulations of mononuclear inflammatory cells in the cerebral cortex.

Thyroid:

No alterations observed.

Most follicles moderate to large in size and lined by flattened cuboidal epithelium.

Activity slight to moderate.

Adrenal:

No alterations observed.

Slight vacuolation of zona fasciculata.

Eye:

No alterations observed.

Artifactual distortion of the cornea and lens.

Lung:

A few lung mite lesions.

Slight amount of brownish, granular, birefringent pigment surrounding small blood vessels, suggestive in appearance of mite pigment.

Occasional small focal proliferation of lymphoreticular cells.

Small area of artifactual collapse.

Liver:

No alterations observed.

Slight vacuolation of hepatocytes throughout the section.

Minimal nonsuppurative pericholangitis characterized by the presence of mononuclear

inflammatory cells.

Occasional focus of necrotic hepatocytes surrounded by mononuclear inflammatory cells.

Slight nonsuppurative pericholangitis.

# GROUP NO. 4 Male Monkey No. 566J (Continued)

GROSS MICROSCOPIC

Kidney:

No alterations observed.

Minimal interstitial nephritis with focal

accumulations of mononuclear inflammatory cells.

Large Intestine:

No alterations observed.

Slight increased numbers of mononuclear

inflammatory cells in the submucosa.

Urinary Bladder:

No alterations observed.

Minimal incidence of focal nonsuppurative

cystitis characterized by accumulations of

mononuclear inflammatory cells in the mucosa and

submucosa.

Testis:

No alterations observed.

Histological appearance typical of immature

testicular tissue.

Prostate:

No alterations observed.

Focal nonsuppurative prostatitis characterized

by focal accumulations of mononuclear

inflammatory cells.

Bone Marrow:

No alterations observed.

Moderately large numbers of maturing elements

of both erythroid and myeloid series.

Slight numbers of megakaryocytes.

The following organs were not altered grossly or microscopically: spinal cord, pituitary, heart, gallbladder, spleen, stomach, pancreas, small intestine, mesenteric lymph node, nerve/muscle, and rib.

## KEY TO DETAILED HISTOPATHOLOGY INCIDENCE TABLE

N = No Section

X = Not Remarkable

A = Autolysis

P or √ = Present or Taken

0 = Absent

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderate to Severe

5 = Severe

## DETAILED HISTOPATHOLOGY INCIDENCE TABLE

	MALES															
			<del></del>		GROUP NUMBER  2 3 4											
			<u> </u>		-				-	3			├		<u>-</u>	
AN IMAL NUMBER	530J	534.3	573.1	581.1	529J	561J	5723	5753	461.1	462.3	4633	571.3	531.7	2603	5653	5663
BRAIN Perivascular Cuffing Glial Nodules	X	P	X	х									Х	х	X	2
SPINAL CORD	X	X	X	X									X	X	X	X
PITUITARY Cysts	X	P	X	X									X	X	X	X
THYROID Level of Activity	2	2	2	2									2-3	2	2	2-3
ADRENAL Vacuolation of Zona Fasciculata	2	2	2-3	2-3	ı								2	2-3	2-3	2
EYE Artifactual Distortion	P	P	P	P									P	P	P	P
HEART Focal Nonsuppurative Myocarditis	X	x	2	X									x	X	x	X
LUNG Artifactual Compression Pigment Lymphoreticular Cell Proliferation	2	2	2 2	2									2	1 2	2 2 2	2 2 2
GALLBLADDER	х	X	x	x									X	X	X	x
SPLEEN Lymphoid Hyperplasia Proliferation of Reticulum Cells	X	P	P	X									x	X	P	X
LIVER Hepatitis Necrosis Pericholangitis Vacuolation	3	3	3	2 2 2-3	2	2	2 1 2-3	2	2 2 2 3	2 2-3	2	2 2	2	2-3	2	2 1 2
Mononuclear Inflammatory Cells Vaculitis	1	2		1					1 P							1

## DETAILED HISTOPATHOLOGY INCIDENCE TABLE

	MALES															
					_			ROUP	NU						,	
			1		┼╌		2				3		+	<del></del>	4	
AN I'MAL AN I'MAL NUMBER	530J	534J	5733	581J	529.1	5613	5723	5753	461 J	4623	4633	571.3	531.1	5603	565J	5663
KIDNEY Intranuclear Inclusion Interstitial Nephritis Regenerative Epithelium Proteinaceous Material in Bowman's Space Mononuclear Inflammatory Cells	x	1	x	2 P	1	x	1	1	P 2 P 2 1	1	х	1	X	x	1	1
STOMACH	x	x	x	x									x	x	x	x
PANCREAS	х	x	x	x									x	x	x	x
SMALL INTESTINE	х	X	X	X									X	x	X	x
LARGE INTESTINE Mononuclear Cell in Submucosa	х	X	X	X									X	X	X	2
MESENTERIC LYMPH NODE	x	x	X	X									X	X	X	X
URINARY BLADDER Cystitis Mononuclear Inflammatory Cells in Submucosa	х	2	1	X									X	x	x	1
TESTIS Immature	P	P	P	P									P	P	P	P
PROSTATE Prostatitis	х	x	X	X									P	N	X	P
NERVE WITH MUSCLE Proliferation of Sarcolemmal Nuclei Fibroplasia Mononuclear Inflammatory Cells	X	X	X	x									5 P 2	X	X	X
RIB	х	X	X	x									X	x	X	x
BONE MARROW Hematogenic Activity	5	5	4	5									5	4	5	4

#### HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date:

November 4, 1969

Material: WR 2529 AK (AF 92486) and WR 2529 RCL

Subject:

REPORT NO. 21

Acute Oral Dose Range - Mice Acute Oral Administration - Mice

Project No. 193-408

Date Received September 3, 1969.

### Description

WR 2529 AK (AF 92486): Fine, white powder with a disagreeable odor.

WR 2529 RCL: White powder with a disagreeable odor.

#### SUMMARY

A preliminary study (administration of each test material to three groups of two adult albino mice each at dosage levels of 100, 1000, and 10,000 mg/kg of body weight) served as an indicator of the acute oral toxicity ranges of WR 2529 AK (AF 92486) and WR 2529 RCL.

Following this preliminary study, each test material was more extensively evaluated for acute oral toxicity by oral intubation to groups of 10 adult albino mice each. WR 2529 AK (AF 92486) was administered to three groups of mice at dosage levels of 6810, 10,000, and 14,700 mg/kg of body weight; WR 2529 RCL was administered to six groups of mice at dosage levels of 2150, 3160, 4640, 6810, 10,000, and 14,700 mg/kg of body weight.

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The acute oral  $LD_{50}$  of WR 2529 AK (AF 92486), obtained from this second study, is 8803 mg/kg of body weight (confidence limits - 7625 mg/kg to 10,164 mg/kg of body weight). The acute oral  $LD_{50}$  of WR 2529 RCL is 9664 mg/kg of body weight (confidence limits - 8412 mg/kg to 11,102 mg/kg of body weight).

#### ACUTE ORAL DOSE RANGE - MICE

Procedure For each compound, oral intubation to three groups of two male rats each at dosage levels of 100, 1000, and 10,000 mg/kg of body weight. Initial weight ranged from 18 to 26 grams, and the animals were fasted overnight prior to dosing. Observations for mortality and signs of effect were made for seven days, the survivors sacrificed (cervical dislocation), and necropsies performed. The diluent for WR 2529 AK (AF 92486) was distilled water; the suspending agent for WR 2529 RCL was a solution of 0.5% carboxymethylcellulose in 0.9% saline.

#### Results

WR 2529 AK (AF 92486):

Mortality Data - One death occurred 24 hours postdose at the 10,000 mg/kg level with no toxic signs observed prior to death.

Principal Toxic Effects - No toxic signs observed.

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Major Necropsy Findings -

(At Death) Pyloric portion of stomach red; small intestines red and containing small amount of fluid; kidneys dark red.

(At Sacrifice) No observable gross pathology.

WR 2529 RCL:

Mortality Data - No deaths occurred at any of the levels tested.

Principal Toxic Effects - No toxic signs observed.

Major Necropsy Findings -

(At Sacrifice) No observable gross pathology.

Procedure WR 2529 AK (AF 92486) was administered by oral intubation to three groups of 10 male rats each (Carbia strain) at dosage levels of 6810, 10,000, and 14,700 mg/kg of body weight; WR 2529 RCL was administered to six groups of 10 male mice each (Carbia strain) at dosage levels of 2150, 3160, 4640, 6810, 10,000, and 14,700 mg/kg of body weight each. The diluent for WR 2529 AK (AF 92486) was distilled water; the suspending agent for WR 2529 RCL was a solution of 0.5% carboxymethylcellulose in 0.9% saline. Initial body weight ranged from 16 to 29 grams, and the animals were fasted overnight prior to dosing.

Observations for mortality and signs of effects were made immediately after dosing; at one, four, and 24 hours; and once daily thereafter for a total of 14 days. Gross necropsy was performed on all animals which died during the study and on those sacrificed (cervical dislocation) at termination. Mortality data was analyzed statistically by the method of Finney, D. J., Probit Analysis, Cambridge University Press, 1952.

#### Results

WR 2529 AK (AF 92486):

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Mortality Data - Values below represent the number of animals dead per number of animals tested, cumulative.

	Concentration of Solution	Time of Death									
Dose		Immediate		Days 2-14							
Dose mg/kg	Z		1	4	24	2-14					
6,810	30	0/10	0/10	1/10	1/10	1/10					
10,000	30	0/10	2/10	2/10	8/10	8/10					
14,700	30	0/10	8/10	10/10							

 $LD_{50}$ , mg/kg - 8803

Confidence Limits (95%), mg/kg - 7625 to 10,164

Major Necropsy Findings -

Slope - 6.094

Graphical presentation of the dose-response analysis is appended to this report.

Principal Toxic Effects - Depression was noted at the 6810 mg/kg level immediately following intubation through Day 2. Depression, labored respiration, ptosis, diarrhea, and hunched appearance (10,000 mg/kg level only) were followed by partial mortality at the 10,000 mg/kg level by 24 hours and total mortality at the 14,700 mg/kg level by four hours. Survivors at the 10,000 mg/kg level appeared normal by Day 6.

(At Death) Stomach and intestines containing yellow fluid resembling compound; pyloric portion of stomach red in appearance; intestines red in appearance; liver and kidneys dark red in color (all observed at the 10,000 and 14,700 mg/kg levels).

(At Sacrifice) No observable gross pathology.

### WR 2529 RCL:

Mortality Data - Values below represent the number of animals dead per number of animals tested, cumulative.

	Concentration	Time of Death									
Dose	of Solution	Immediate		Hours		Days					
mg/kg	*		1	4	24	2-14					
2,150	30	0/10	0/10	0/10	0/10	0/10					
3,160	30	0/10	0/10	0/10	0/10	0/10					
4,640	30	0/10	0/10	0/10	0/10	0/10					
6,810	30	0/10	0/10	0/10	0/10	0/10					
10,000	30	0/10	0/10	0/10	6/10	6/10					
14,700	30	0/10	7/10	8/10	10/10						

 $LD_{50}$ , mg/kg - 9664

Confidence Limits (95%), mg/kg - 8412 to 11,102

Slope - 6.208

Graphical presentation of the dose-response analysis is appended to this report.

Principal Toxic Effects - No toxic signs were noted at the 2150 and 3160 mg/kg levels. Toxic signs were evident at the 4640, 6810, and 10,000 mg/kg levels by four or 24 hours postdose and included the following: depression, squinting, hunched appearance (6810 and 10,000 mg/kg levels only), piloerection (6810 and 10,000 mg/kg levels only), diarrhea (10,000 mg/kg level only), and labored respiration (10,000 mg/kg level only). Animals at the 4640 and 6810 mg/kg levels appeared normal by Day 4 and survivors at the 10,000 mg/kg level appeared normal by Day 7. At the 14,700 mg/kg level, depression, diarrhea, labored respiration, and ptosis were noted immediately or one hour following intubation and were followed by total mortality at 24 hours.

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Major Necropsy Findings -

(At Death) Stomach and intestines distended with white fluid resembling compound (10,000 and 14,700 mg/kg levels); stomach lining thin in appearance (10,000 mg/kg level); stomach and intestines blanched and smooth (14,700 mg/kg level); pyloric portion of stomach dark red (14,700 mg/kg level); liver and kidneys dark red (14,700 mg/kg level).

(At Sacrifice) No observable gross pathology.

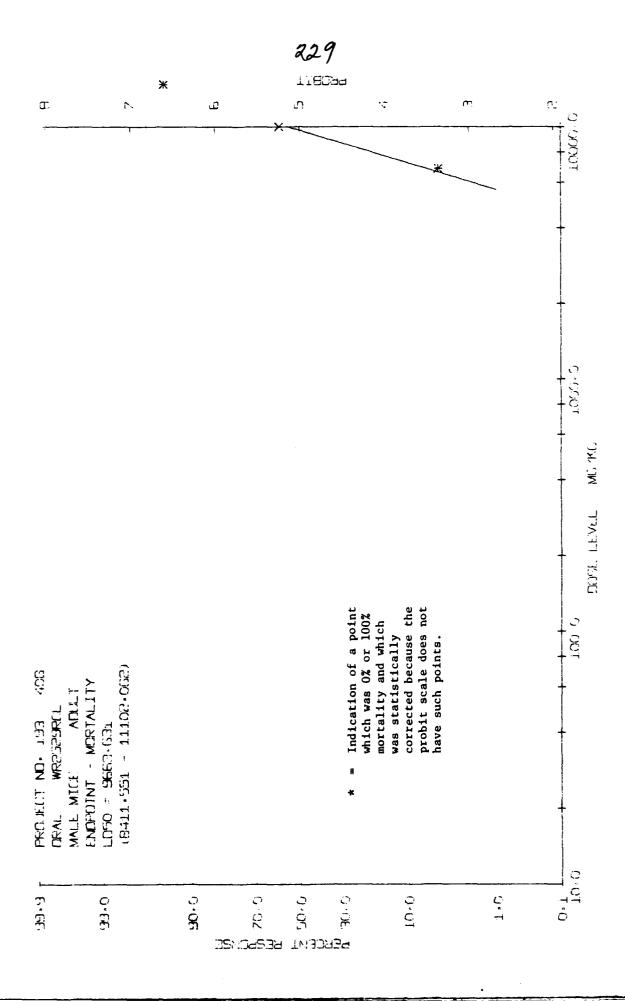
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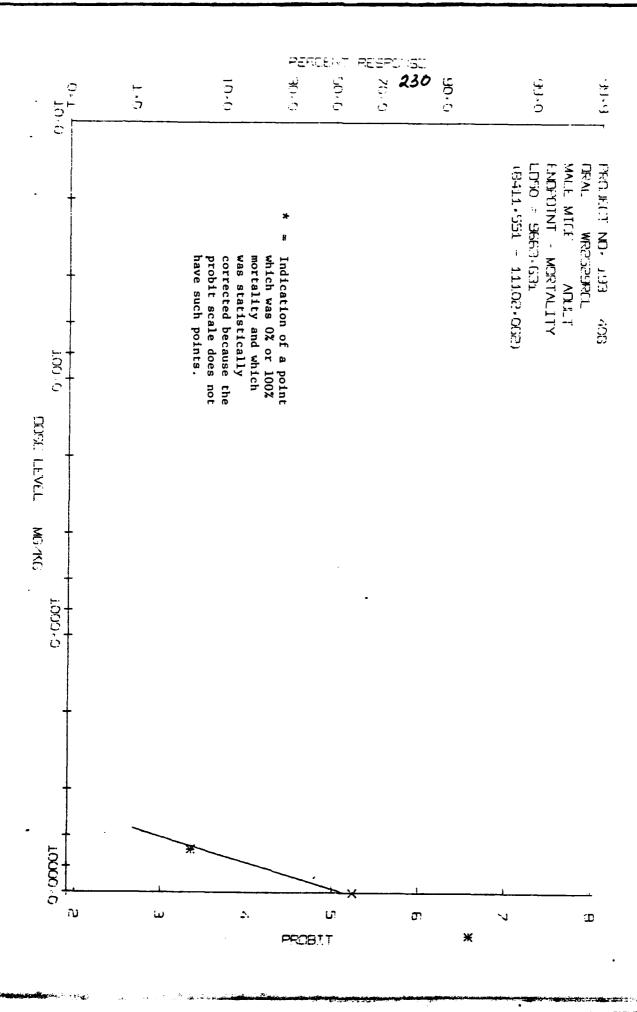
MARCELINA B. POWERS, D.V.M., M.S. Project Manager, Drugs and

Industrial Chemicals Toxicology-Bioscience Laboratory

Report Preparation: Lambert Supervision: Fink

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#### HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: November 19, 1969

Material: WR 2823 (AU 69115)

Subject: REPORT NO. 23

Acute Oral - Mice Project No. 193-409

Date Received September 18, 1969.

Description Fine, white powder with no noticeable odor.

Purity Assumed to be 100% active ingredient.

#### SUMMARY

WR 2823 (AU 69115) was evaluated for acute oral toxicity by gastric intubation to six groups of 10 male albino mice each. The acute oral LD<sub>50</sub> of the compound was 940 mg/kg of body weight (confidence limits, 760 to 1163 mg/kg of body weight). Toxic effects produced by WR 2823 (AU 69115) consisted of depression, labored respiration, ptosis, comatose appearance, intermittent tremors, and cold to touch.

#### **PROCEDURE**

The compound was administered by oral intubation to six groups of 10 male mice (Carbia strain) each. The solvent was distilled water. Initial body weight ranged from 18 to 27 grams, and the animals were fasted overnight prior to dosing. Observations for mortality and signs of effects were made immediately

after dosing; at one, four, and 24 hours; and once daily thereafter for a total of 14 days. Gross necropsy was performed on all animals which died during the study and on those sacrificed (cervical dislocation) at termination. Mortality data were analyzed statistically by the method of Litchfield, J. T., and Wilcoxon, F., J. Pharmacol. Exptl. Therap., 96, 99, 1949.

Mortality Data Values below represent the number of animals dead per number of animals tested, cumulative.

	Concentration	Time of Death								
Dose mg/kg	of Solution Z	Immediate	Hours 1-24	Days 2-14						
100	1	0/10	0/10	1/10*						
159	1	0/10	0/10	0/10						
251	1	0/10	0/10	0/10						
398	1	0/10	0/10	1/10*						
631	2	0/10	0/10	0/10						
1000	2	0/10	5/10	6/10						

 $LD_{50}$ , mg/kg - 940

Confidence Limits (95%), mg/kg - 760 to 1163

Slope - 6.433

<sup>\*</sup> These deaths were considered incidental and were not used in  $LD_{50}$  calculations. Graphical presentation of the dose-response analysis is appended to this report.

TRWA LIFE SCIENCES CENTER

Principal Toxic Effects One death on Day 4 at the 100 mg/kg level and one death on Day 9 at the 398 mg/kg level, both preceded by hunched appearance, were considered to be incidental deaths. Animals at the 251 and 398 mg/kg levels exhibited piloerection and depression through four or 48 hours. Depression, labored respiration, ptosis, comatose appearance, intermittent tremors, and cold to touch were signs noted prior to partial mortality by 48 hours at the 1000 mg/kg level. Survivors at this level appeared hunched and thin through Day 9.

### Major Necropsy Findings

At Death: Lungs dark red in color (100 mg/kg level); clear, yellowish fluid in stomach (1000 mg/kg level); stomach lining smooth and thin (1000 mg/kg level); blood vessels in stomach and intestinal tract dilated (1000 mg/kg level); renal cortex and medulla dark red with no differentiation between cortex and medulla (1000 mg/kg level).

At Sacrifice: No gross pathology noted.

Submitted by

MARCELINA B. POWERS, D.V.M., M.S.

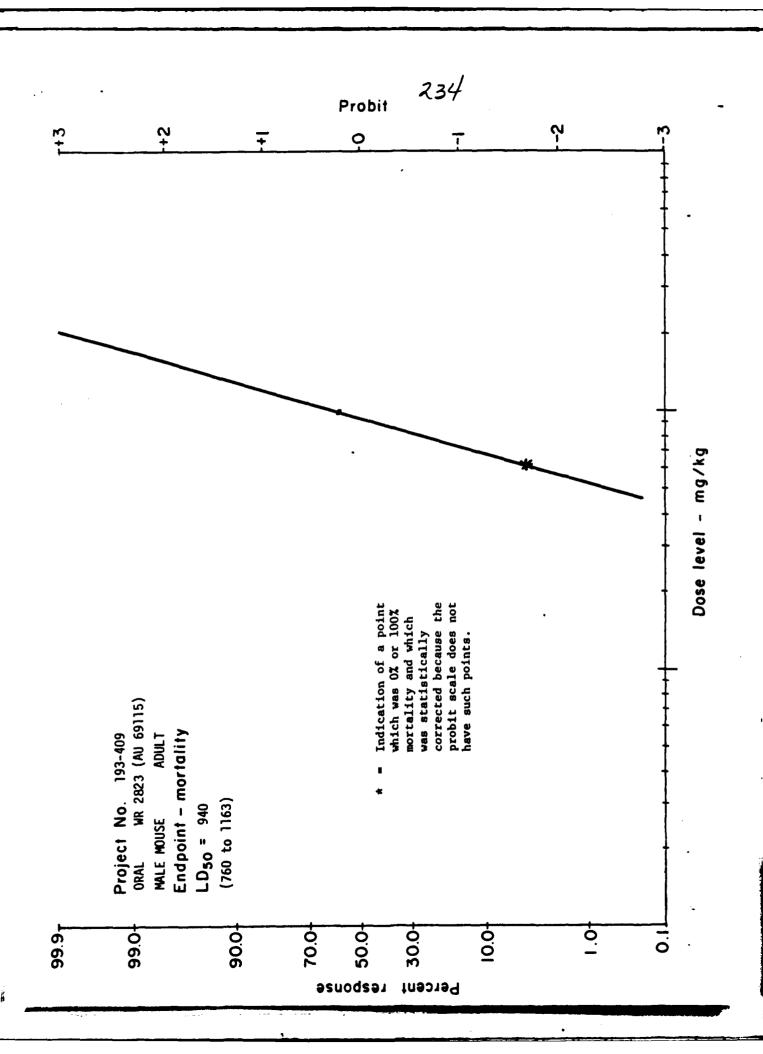
Project Manager, Drugs and Industrial Chemicals

Toxicology-Biosciences Laboratory

Report Preparation: Lambert

Supervision: Fink

njm



#### HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: September 23, 1970

Material:

WR-2823 (AU 69115)

Subject:

REPORT NO. 36

Pathology Report

Two-Week Intravenous Toxicity Study - Rats

Project No. 193-410

This pathology report is a supplement to Report No. 31 dated, January 23, 1970, entitled "Two-Week Intravenous Toxicity Study - Rats" on compound, WR-2823 (AU 69115). In that report the results were reported without the histopathologic evaluation of tissues.

Submitted b

PRODERICK E. RENO, Ph.D. Project Manager, Drugs and

Industrial Chemicals Department
Toxicology-Biosciences Laboratory

Pathology by

ROBERT P. KWAPIEN, D.V.M., Ph.D.

Staff Pathologist

gbb

## HISTOPATHOLOGICAL EVALUATION OF MALE AND FEMALE ALBINO RATS SACRIFICED AT TERMINATION

WR-2823 (AU 69115) GROUP NO. 1 Male Rat No. 82-969

**GROSS** 

MICROSCOPIC

Brain:

No alterations observed.

Slight nonsuppurative meningocephalitis.

Slight focal gliosis.

Spinal Cord:

No alterations observed.

In gray matter of one spinal cord section an

area of focal gliosis.

Pituitary:

No alterations observed.

Only pars distalis included in section.

Otherwise, not remarkable.

Thyroid:

No alterations observed.

Chiefly, medium- and large-sized follicles.

Follicular epithelium chiefly low cuboidal

or cuboidal.

Activity moderate.

Adrenal:

No alterations observed.

Minimal vacuolation of cells in zona

fasciculata.

Eye:

No alterations observed.

Some shatter of the lense and artifactual

displacement of retina.

Section does not included optic nerve.

Otherwise, not remarkable.

## GROUP NO. 1 Male Rat No. 82-696 (Continued)

GROSS

MICROSCOPIC

Heart:

No alterations observed.

Minimal interstitial myocarditis.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Minimal peribronchial lymphoid hyperplasia.

Spleen:

No alterations observed.

Slight extramedullary hematopoiesis.

Liver:

No alterations observed.

Minimal chronic pericholangitis.

Occasional foci of nonsuppurative hepatitis

with a component of histiocytic cells.

Kidney:

No alterations observed.

Slight interstitial nephritis.

Occasional foci of regenerating tubular

epithelium.

Pancreas:

No alterations observed.

Slight chronic pancreatitis.

Large Intestine:

No alterations observed.

Nematodiasis.

Mesenteric Lymph Node:

No alterations observed.

Section not available for examination.

Testis:

No alterations observed.

Activity appeared to be within normal limits.

# GROUP NO. 1 Male Rat No. 82-696 (Continued)

GROSS (CONCINCED)

MICROSCOPIC

Bone Marrow:

No alterations observed.

Moderate numbers of megakaryocytes.

Moderate numbers of maturing erythroid and

myeloid cells.

Activity appeared to be within normal limits.

Section rather small.

The following organs were not altered grossly or microscopically: stomach, small intestine, urinary bladder, prostate, and bone.

### GROUP NO. 1 Male Rat No. 82-700

GROSS

MICROSCOPIC

Pituitary:

No alterations observed.

Small, dilated space present between pars intermedia and pars distalis which contained small numbers of unidentifiable cells, erythrocytes, and eosinophilic material.

Thyroid:

No alterations observed.

Small- and large-sized follicles present with

small follicles predominating.

Epithelium lining follicles chiefly cuboidal

or high cupoidal.

Activity judged to be moderately high.

Adrenal:

No alterations observed.

Moderate vacuolation of cells in zona fasciculata.

Eye:

No alterations observed.

Cornea folded.

Segments of iris, ciliary process, and retina

missing.

Section does not include optic nerve.

Remaining tissues not remarkable.

Heart:

No alterations observed.

Moderate chronic myocarditis and endocarditis.

One rather large focus of chronic inflammation

present in which many histiocytes and

mononuclear cells infiltrated the myocardium

and endocardium.

# GROUP NO. 1 Male Rat No. 82+/00 (Continued)

GROSS

MICROSCOPIC

In affected areas, a few degenerating myocardial fibers persist.

Mild chronic epicarditis.

Lung:

Dark red areas on all

lobes.

Slight interstitial penumonitis.

Moderate peribronchiolar lymphoid hyperplasia.

Spleen:

No alterations observed.

Slight numbers of extramedullary hematopoetic

foci.

Liver:

Left lateral lobe contained

small, yellow foci.

Occasional foci of nonsuppurative hepatitis.

Focal vacuolation of liver cells suggesting

lipoidosis.

Large Intestine:

No alterations observed.

Nematodiasis.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared to be within normal limits.

## GROUP NO. 1 Male Rat No. 82-700 (Continued)

GROSS

Testis:

No alterations observed.

Activity appeared within normal limits.

MICROSCOPIC

Bone Marrow:

No alterations observed.

Many megakaryocytes present.

Numerous maturing myeloid and erythroid

cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal cord, kidney, stomach, pancreas, small intestine, urinary bladder, prostate, and bone.

### GROUP NO. 1 Male Rat No. 82-702

GROSS Male Rat No. 82-/02

MICROSCOPIC

Brain:

No alterations observed.

Slight nonsuppurative meningoencephalitis,

perivascular cuffing, and focal gliosis.

Spinal Cord:

No alterations observed.

Focal nonsuppurative meningitis.

Pituitary:

No alterations observed.

Only pars distalis included in section.

Otherwise, not remarkable.

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles

present.

Epithelium lining follicles chiefly cuboidal.

Activity moderate.

Adrenal:

No alterations observed.

Adrenal medulla not included in section.

Moderate vacuolation of cells in zona fasciculata.

Eye:

No alterations observed.

Optic nerve not included on section.

Otherwise, not remarkable.

Heart:

No alterations observed.

Slight chronic myocarditis, epicarditis, and

endocarditis.

Lung:

No alterations observed.

Moderate interstitial pneumonitis.

Mild peribronchiolar lymphoid hyperplasia.

# GROUP NO. 1 Male Rat No. 82-702 (Continued)

GROSS

MICROSCOPIC

Spleen:

Appeared enlarged.

Moderate to slight extramedullary hematopoietic

activity.

Liver:

No alterations observed.

Slight focal nonsuppurative hepatitis.

Slight chronic pericholangitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis.

Small areas of tubular regeneration in cortex.

Slight chronic pyelitis.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared within normal limits.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: stomach, pancreas, small intestine, large intestine, urinary bladder, testis, prostate, and bone.

### GROUP NO. 1 Male Rat No. 82-703

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Slight nonsuppurative meningocephalitis.

Slight focal gliosis.

Spinal Cord:

No alterations observed.

One section of spinal cord incomplete.

Otherwise, not remarkable.

Thyroid:

No alterations observed.

Small-, medium, and large-sized follicles with

the small follicles predominating.

Epithelium lining follicles chiefly cuboidal.

Activity moderate.

Adrenal:

No alterations observed.

Slight generalized vacuolation of cells in

zona fasciculata.

Eye:

No alterations observed.

Section of optic nerve not included.

Otherwise, not remarkable.

Heart:

No alterations observed.

Slight myocarditis and epicarditis chronic

in nature.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Slight perivascular lymphoid hyperplasia.

Spleen:

Appeared slightly enlarged.

Slight to moderate extramedullary hematopoietic

activity.

GROUP NO. 1
Male Rat No. 82-703 (Continued)

GROSS MICROSCOPIC

Liver:

No alterations observed.

Slight chronic pericholangitis.

Slight focal nonsuppurative hepatitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis.

Pancreas:

No alterations observed.

Minimal nonsuppurative pancreatitis.

Urinary Bladder:

No alterations observed.

Minimal nonsuppurative cystitis.

Mesenteric Lymph Node:

No alterations observed.

Moderate erythrophagia seen in medullary

sinusoids.

Perivascular chronic inflammation of a few

vessels.

Testis:

No alterations observed.

Activity appeared to be within normal limits.

Prostate:

No alterations observed.

Section not available for examination.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Moderately high numbers of maturing erythroid

and myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: pituitary, stomach, small intestine, large intestine, and bone.

## GROUP NO. 1 Male Rat No. 82-704

**GROSS** 

MICROSCOPIC

Brain:

No alterations observed.

Slight focal meningocephalitis with the

abscence of focal gliosis.

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles flattened or

low cuboidal.

Activity low.

Adrenal:

No alterations observed.

Slight vacuolation of cells in zona fasciculata.

Otherwise, not remarkable.

Eye:

No alterations observed.

Slight nonsuppurative myositis involving

extra ocular muscles in the posterior segment

of the globe.

Section does not include optic nerve.

Otherwise, not remarkable.

Heart:

No alterations observed.

Minimal chronic myocarditis.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Slight peribronchiolar lymphoid hyperplasia.

Spleen:

Appeared slightly enlarged.

Moderate to moderately high extramedullary

hematopoietic activity.

GROUP NO. 1
Male Rat No. 82-704 (Continued)

GROSS MICROSCOPIC

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Slight chronic pericholangitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis.

Pancreas:

No alterations observed.

Poor histologic section, many wrinkles and folds.

Minimal focal chronic pancreatitis.

Urinary Bladder:

No alterations observed.

Lumen very distended.

Otherwise, not remarkable.

Mesenteric Lymph Node:

No alterations observed.

Section of node missing.

Testis:

No alterations observed.

Slight testicular tubular degeneration.

Slight nonsuppurative orchitis.

Bone Marrow:

No alterations observed.

Section too small to conduct a meaningful

histopathological evaluation.

The following organs were not altered grossly or microscopically: spinsl cord, pituitary, adrenal, stomach, small intestine, large intestine, prostate, and bone.

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, medium- and large-sized follicles.

Epithelium lining follicles often flattened or

low cuboidal.

Activity low.

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic

activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Considerable numbers of maturing erythroid and

myeloid cells.

Activity moderate.

The following organ was not altered grossly or microscopically: kidney.

GROSS Male Rat No. 82-/1

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles chiefly low

cuboidal.

Activity low.

Lung:

Small consolidated areas.

Moderate interstitial pneumonitis.

Spleen:

Appeared enlarged.

Slight extramedullary hematopoietic activity.

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Occasional chronic pericholangitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis.

Occasional foci of regenerative tubular

epithelium.

Small focus of chronic inflammation seen

in perirenal fat.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Several numbers of maturing erythroid and

myeloid cells.

Activity moderately high.

GROSS AZ=718

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium chiefly low cuboidal or cuboidal.

Activity low.

Lung:

Dark red areas in all lobes.

Moderate interstitial pneumonitis.

Moderate perivascular cuffs of lymphocytic

cells.

Large areas of focal hemorrhage.

Some bronchi contained aspirated blood.

Spleen:

Appeared enlarged.

Slight to moderate extramedullary hematopoietic

activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Kidney:

No alterations observed.

Moderate chronic interstitial nephritis.

In some areas, mild dilatation of some cortical

tubules.

These tubules usually empty but, in some cases

contained very small amounts of granular

eosinophilic material.

Slight to moderate tubular regenerative changes.

Slight chronic pyelitis.

GROUP NO. 2
Male Rat No. 82-718 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Numerous megakaryocytes seen.

Considerable numbers of maturing erythroid and

myeloid cells.

Activity moderate.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, small-, and medium-sized follicles.

Epithelium lining the follicles varied from

cuboidal to high cuboidal.

Activity moderately high.

Spleen:

No alterations observed.

Moderately high extramedullary hematopoietic

activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Kidney:

Speckled surface pale

yellowish brown.

Moderate chronic interstitial nephritis

involving cortex and medulla.

Focal areas of tubular regeneration, moderate

in extent, and sometimes accompanied by slightly

dilated tubules.

Cervical Lymph Node:

Appeared enlarged and dark

pink.

Lymphoid follicles very active and merged one

with another.

Many plasma cells present in the medullary

sinusoids.

Node congested.

## GROUP NO. 2 Male Rat No. 82-719 (Continued)

**GROSS** 

MICROSCOPIC

Some large sections of salivary glands submitted along with lymph node section, these sections not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderate.

GROSS

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

MICROSCOPIC

Epithelium flattened to low cuboidal.

Activity low.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Kidney:

No alterations observed.

Some tubules in medulla appeared dilated.

Otherwise, not remarkable.

Small Intestine:

Wall appeared thickened.

Not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderate.

The following organ was not altered grossly or microscopically: liver.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles flattened

or low cuboidal.

Activity low.

Lung:

Small, gray, cyst-like

areas in all lobes.

Slight interstitial pneumonitis.

Slight perivascular lymphocytic infiltration.

Large areas of congestion in focal pattern.

Spleen:

No alterations observed.

Slight extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Liver:

Small, firm, yellow area

in median lobe.

Section preserved.

Area seen grossly represented by a focus

of chronic inflammation and fibrosis with

bile duct hyperplasia.

Minimal focal nonsuppurative hepatitis.

Kidney:

No alterations observed.

Very minimal tubular regenerative changes.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, small- and medium-sized follicles.

Epithelium lining the follicles cuboidal or

plump cuboidal.

Activity moderately high.

Lung:

Consolidated area in

left lobe.

Slight interstitial pneumonitis.

Slight bronchiectasis with purulent exudate

in a few bronchi and bronchioles.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal amount of pigment in red pulp.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Minimal chronic pericholangitis.

Kidney:

No alterations observed.

Very minimal interstitial nephritis.

Otherwise, not remarkable.

Stomach:

Walls thickened.

Slight chronic gastritis.

Focal collections of chronic inflammatory cells

in the submucosa.

## GROUP NO. 3 Male Rat No. 82-738 (Continued)

GROSS

MICROSCOPIC

Small Intestine:

Walls thickened and yellow

foci in lining.

Not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Considerable numbers of maturing erythroid

and myeloid cells.

Activity moderately high.

GROSS Male Rat No. 82-739

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles chiefly cuboidal

in nature.

Activity moderate.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Minimal chronic pericholangitis.

Small Intestine:

Small, white foci in

lining.

Not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

The following organ was not altered grossly or micorscopically: kidney.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Many small- and medium-sized follicles.

Epithelium lining the follicles chiefly

cuobidal in type.

Activity moderate.

Lung:

Consolidated areas in

all lobes.

Moderate interstitial pneumonitis.

Peribronchiolar and perivascular lymphoid

proliferation.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment in red pulp.

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Minimal chronic pericholangitis.

Kidney:

No alterations observed.

Slight interstitial nephritis involving cortex

and medulla.

Minimal numbers of regenerating tubules.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles chiefly

flattened or low cuboidal.

Activity moderate.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Kidney:

Greenish tinge.

Very mild nonsuppurative pyelitis.

Otherwise, not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, large- and medium-sized follicles.

Epithelium lining follicles flattened or

low cuboidal in type.

Activity low.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic

activity.

Small Intestine:

Duodenum walls thickened with

small, yellow foci.

Not remarkable.

Kidney:

No alterations observed.

Slight tubular regenerative activity.

Prostate:

No alterations observed.

Slight suppurative prostatitis with

accumulations of purulent exudate within

some prostatic glands.

## GROUP NO. 4 Male Rat No. 82-758 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

Noalterations observed.

Numerous megakaryocytes.

Moderate numbers of maturing erythroid and

myeloid cells.

Activity moderate.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, eye, heart, liver, stomach, pancreas, large intestine, urinary bladder, mesenteric lymph node, testis, and bone.

GROSS MICROSCOPIC

Thyroid:

No alterations observed.

Large- and medium-sized follicles predominated.

Epithelium varied from flattened to cuboidal.

Activity judged to be low.

Eye:

No alterations observed.

Many artifacts present.

Portions of retina, ciliary processes, iris

and cornea, missing.

Lung:

Dark red areas in all lobes.

Slight interstitial pneumonitis.

Moderate cuffs of lymphocytic cells around

blood vessels and bronchioles.

Spleen:

No alterations observed.

Minimal extramedullary hematopoietic activity.

Prostate:

No alterations observed.

Section not available for examination.

Bone Marrow:

No alterations observed.

Moderate numbers of megakaryocytes.

Moderate numbers of maturing erythroid and

myeloid cells.

Activity moderate.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, heart, liver, kidney, stomach, pancreas, small intestine, large intestine, urinary bladder, mesenteric lymph node, testis, and bone.

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles chiefly low

cuboidal or cuboidal.

Activity moderate.

Heart:

No alterations observed.

Minimal focal chronic myocarditis.

Lung:

Dark red areas in all lobes.

Minimal interstitial pneumonitis.

Large foci of hemorrhage and pulmonary edema.

Some bronchi and alveolar lumens contained

aspirated blood.

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic

activity.

Liver:

No alterations observed.

Slight chronic pericholangitis.

Minimal nonsuppurative hepatitis.

Kidney:

No alterations observed.

Occasional foci of chronic interstitial nephritis.

Minimal nonsuppurative pyelitis.

Pancreas:

No alterations observed.

Minimal chronic interstitial pancreatitis.

Mesenteric Lymph Node:

No alterations observed.

. No section available for examination.

GROUP NO. 4
Male Rat No. 82-760 (Continued)

MICROSCOPIC

Urinary Bladder:

No alterations observed.

**GROSS** 

Minimal focal nonsuppurative cystitis.

Testis:

No alterations observed.

Minimal nonsuppurative epididymis with small

collections of chronic inflammatory cells in

the interstitium.

Bone Marrow:

No alterations observed.

Marrow section insufficient for critical

evaluation.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, eye, stomach, small intestine, large intestine, prostate, and bone.

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles chiefly low

cuboidal.

Activity moderate.

Heart:

No alterations observed.

Minimal chronic myocarditis.

Lung:

Small, gray, cyst-like

areas in all lobes.

Slight chronic interstitial pneumonitis.

Bronchioles appeared widely dilated.

Some collapse of the pulmonary parenchyma.

Spleen:

No alterations observed.

Very minimal extramedullary hematopoietic

activity.

Kidney:

Pale yellowish brown

cortex.

Dark pink outer medulla.

Not remarkable.

Testis:

No alterations observed.

Minimal nonsuppurative epididymitis.

Bone Marrow:

No alterations observed.

Moderate numbers of megakaryocytes.

Moderate numbers of maturing erythroid and

myeloid cells.

Activity moderate.

# GROUP NO. 4 Male Rat No. 82-764 (Continued)

ROSS MICROSCOPIC

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, eye, liver, stomach, pancreas, small intestine, large intestine, urinary bladder, mesenteric lymph node, prostate, and bone.

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles flattened or

low cuboidal.

Activity low.

Lung:

Gray, cyst-like areas

in all lobes.

Slight interstitial pneumonitis.

Slight peribronchiolar lymphoid hyperplasia.

Spleen:

No alterations observed.

Slight extramedullary hematopoietic activity.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Kidney:

Small, yellowish brown

cortex.

Dark red medulla.

Minimal tubular regeneration.

Otherwise, not remarkable.

Bone Marrow:

No alterations observed.

Moderate numbers of megakaryocytes.

Moderate numbers of maturing erythroid and

myeloid cells.

Activity moderate.

# GROUP NO. 4 Male Rat No. 82-765 (Continued)

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MICROSCOPIC

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, eye, heart, stomach, pancreas, small intestine, large intestine, urinary bladder, mesenteric lymph node, testis, prostate, and bone.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, moderate-sized follicles.

Epithelium lining follicles chiefly low cuboidal.

Activity low.

Adrenal:

No alterations observed.

Medulla not included in section.

Moderate vacuolation of cells in zona

fasciculata.

Eye:

No alterations observed.

Optic nerve not included in section.

Otherwise, not remarkable.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Moderate peribronchial lymphoid hyperplasia.

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic

activity.

Liver:

No alterations observed.

Minimal chronic pericholangitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis with

accompaning slight tubular regeneration.

Small Intestine:

No alterations observed.

Section not available for examination.

## GROUP NO. 5 Male Rat No. 82-776 (Continued)

GROSS

MICROSCOPIC

Mesenteric Lymph Node:

No alterations observed.

Activity appeared to be within normal limits.

Cervical Lymph Node:

Enlarged.

Slight follicular hyperplasia.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous, maturing erythroid and myeloid cells.

Activity moderate.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, stomach, pancreas, large intestine, urinary bladder, testis, prostate, and bone.

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Mild nonsuppurative meningitis of the cerebellar

cortex.

Pituitary:

No alterations observed.

Not remarkable.

Small section; pars nervosa and pars intermedia

missing.

Thyroid:

No alterations observed.

Chiefly, medium- and large-sized follicles.

Epithelium lining follicles chiefly cuboidal or

high cuboidal.

Activity moderately high.

Adrenal:

No alterations observed.

Moderate vacuolation of zona fasciculata.

Eye:

No alterations observed.

Lens badly shattered.

Optic nerve not included in section.

Otherwise, not remarkable.

Heart:

No alterations observed.

Slight focal myocarditis and epicarditis.

Lung:

No alterations observed.

Minimal interstitial pneumonitis.

Slight peribronchial lymphoid hyperplasia.

Moderate alveolar expansion.

GROUP NO. 5
Male Rat No. 82-778 (Continued)

\_\_\_\_\_

**GROSS** 

MICROSCOPIC

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic

activity.

Kidney:

No alterations observed.

Slight focal, chronic interstitial nephritis.

Slight focal pyelitis.

Cervical Lymph Node:

Enlarged.

Cervical lymph nodes not found in section, but

sections of salivary gland present.

Urinary Bladder:

No alterations observed.

Poor histologic section.

Mucosa very folded.

Slight focal nonsuppurative cystitis.

Liver:

No alterations observed.

Slight chronic pericholangitis.

Occasional focus of nonsuppurative hepatitis

with a few necrotic hepatocytes.

Prostate:

No alterations observed.

Section not available for examination.

Bone Marrow:

No alterations observed.

Moderate numbers of megakaryocytes.

Considerable numbers of maturing erythroid

and myeloid cells.

Activity moderate.

The following organs were not altered grossly or microscopically: spinal cord, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, testis, and bone.

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Mild nonsuppurative meningocephalitis

characterized by small foci of gliosis,

collections of small numbers of

lymphocytes within the meninges, and occasional

cuffing of intracerebral vessels by chronic

inflammatory cells.

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles chiefly cuboidal.

Activity moderate.

Adrenal:

No alterations observed.

Slight vacuolation of cells in zona fasciculata.

Eye:

No alterations observed.

Portions of the anterior segment of eye missing;

iris and cornea cannot be evaluated

microscopiclly.

Other segments of eye normal.

Heart:

No alterations observed.

Minimal focal, chronic myocarditis.

Chronic inflammatory cells occured in

interstitial locations of the myocardium.

GROUP NO. 5
Male Rat No. 82-780 (Continued)

GROSS MICROSCOPIC

Lung:

Dark red areas on all lobes.

Mild interstitial pneumonitis.

Mild peribronchial lymphoid hyperplasia.

Spleen:

No alterations observed.

Activity appeared within normal limits.

Liver:

No alterations observed.

Minimal focal chronic pericholangitis.

Kidney:

No alterations observed.

Minimal focal chronic pyelitis.

Pancreas:

No alterations observed.

Minimal focal chronic pancreatitis.

Small Intestine:

No alterations observed.

The superficial mucosal epithelium missing.

Urinary Bladder:

No alterations observed.

No section available for examination.

Mesenteric Lymph Node:

No alterations observed.

Small section submitted.

Activity appeared within normal limits.

Testis:

No alterations observed.

Activity appeared within normal limits.

Prostate:

No alterations observed.

No section available for examination.

## GROUP NO. 5 Male Rat No. 82-780 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Cytologic staining poor, probably due to

over decalcification.

Numerous numbers of megakaryocytes.

Poor cytologic detailed prevents a definitive

evaluation of hematogenic activity.

The marrow, however, appeared very cellular.

The following organs were not altered grossly or microscopically: spinal cord, pituitary, adrenal, stomach, large intestine, and bone.

GROSS \_\_\_\_

MICROSCOPIC

Brain:

No alterations observed.

Minimal nonsuppurative meningoencephalitis.

Focal glial nodules within brain.

Minimal numbers of intracerebral vessels

cuffed by lymphocytes.

Small numbers of lymphocytes present in

the meninges.

Pituitary:

No alterations observed.

Small section included.

Only pars distalis included on section.

Otherwise, not remarkable.

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles chiefly cuboidal in

type.

Activity moderate.

Adrenal:

No alterations observed.

only small section of medullary area included.

Slight vacuolation of cells in zona fasciculata.

Eye:

No alterations observed.

Minimal chronic dacryoadenitis.

Otherwise, not remarkable.

## GROUP NO. 5 Male Rat No. 82~782 (Continued)

GROSS (CONCERNO)

Heart:

No alterations observed.

Minimal nonsuppurative myocarditis.

Lung:

No alterations observed.

Minimal intestitial pneumonitis and peri-

MICROSCOPIC

bronchial lymphoid hyperplasia.

Spleen:

Appeared enlarged.

Moderate extramedullary hematopoiesis.

Liver:

No alterations observed.

Mild chronic pericholangitis.

Kidney:

No alterations observed.

Occasional foci of chronic interstitial

nephritis.

Small numbers of regenerating tubules in

affected areas.

Pancreas:

No alterations observed.

Minimal chronic pancreatitis with focal

acinar atrophy.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared within normal limits.

Adventitia of one artery in mesenteric fat

was segmentally infiltrated with collections

of mononuclear inflammatory cells and a

few polymorphs.

Testis:

No alterations observed.

Activity appeared within normal limits.

## GROUP NO. 5 Male Rat No. 82-782 (Continued)

GROSS

MICROSCOPIC

#### Bone Marrow:

No alterations observed.

Moderately high numbers of megakaryocytes.

Moderately high numbers of maturing erythroid

and myeloid cells.

Activity moderately high.

#### Prostate:

No alterations observed.

Section not available for examination.

The following organs were not altered grossly or microscopically: spinal cord, stomach, small intestine, large intestine, urinary bladder, and bone.

CROSS

MICROSCOPIC

Brain:

No alterations observed.

Mild nonsuppurative meningitis.

Rarely, a small focus of gliosis.

Pituitary:

No alterations observed.

Section incomplete.

Only the pars distalis included.

Otherwise, not remarkable.

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles chiefly cuboidal

in size.

Activity moderate.

Adrenal:

No alterations observed.

Medulla not included on section.

Low level of vacuolation of cells in zona

fasciculata.

Heart:

No alterations observed.

Minimal chronic myocarditis.

Lung:

No alterations observed.

Minimal interstitial pneumonitis and

peribronchial lymphoid hyperplasia.

Spleen:

Appeared enlarged.

Moderate extramedullary hematopoietic activity.

Liver:

No alterations observed.

Minimal chronic pericholangitis.

## GROUP NO. 5 Male Rat No. 82-785 (Continued)

GROSS (Continued)

MICROSCOPIC

Kidney:

No alterations observed.

Minimal chronic interstitial nephritis and

focal chronic pyelitis.

Pancreas:

No alterations observed.

Minimal chronic pancreatitis.

Mesenteric Lymph Node:

No alterations observed.

Small section submitted.

Activity appeared to be within normal limits.

One mesenteric artery had infiltrations of

mononuclear cells and polymorphs in the

adventitia in a segmental distribution.

Testis:

No alterations observed.

Activity appeared within normal limits.

Bone Marrow:

No alterations observed.

Moderately high numbers of megakaryocytes.

Moderately high numbers of maturing erythroid

and myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: spinal cord, eye, stomach, small intestine, large intestine, urinary bladder, prostate, and bone.

GROUP NO. 1 Female Rat No. 82-706

**GROSS** 

MICROSCOPIC

Brain:

No alterations observed.

Slight nonsuppurative meningocephalitis,

perivascular cuffing, and focal gliosis.

Spinal Cord:

No alterations observed.

Minimal nonsuppurative meningomyelitis.

Thyroid:

No alterations observed.

Section not available for examination.

Adrenal:

No alterations observed.

Medulla not included.

Moderate vacuolation of cells in the zona

fasciculata.

Heart:

No alterations observed.

Minimal nonsuppurative myocarditis and

epicarditis.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Slight perivascular lymphoid hyperplasia.

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic

activity.

Pigment in red pulp minimal in amount.

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Kidney:

No alterations observed.

Minimal tubular dilatation of medullary tubule.

GROUP NO. 1
Female Rat No. 82-706 (Continued)

GROSS MICROSCOPIC

Urinary Bladder:

No alterations observed.

Minimal nonsuppurative cystitis.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared to be within normal limits.

Ovary:

No alterations observed.

Activity appeared to be witin normal limits.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes present.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: pituitary, eye, stomach, pancreas, small intestine, large intestine, uterus, and bone.

GROSS Female Rat No. 82-

MICROSCOPIC

Pituitary:

No alterations observed.

Pars nervosa and pars intermedia not included

in section.

Pars distalis, not remarkable.

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles varied from flattened

to cuboidal.

Activity low.

Adrenal:

No alterations observed.

Moderate diffuse vacuolation of zona

fasciculata.

Eye:

No alterations observed.

Cornea and parts of retina and iris are missing.

Section does not include optic nerve.

Otherwise, not remarkable.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Slight perivascular lymphoid hyperplasia.

Spleen:

No alterations observed.

Minimal extramedullary hematopoietic activity.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared within normal limits.

## GROUP NO. 1 Female Rat No. 82-707 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Complete maturation of myeloid and erythroid

cells.

Numerous megakaryocytes.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal cord, heart, liver, kidney, stomach, pancreas, small intestine, large intestine, urinary bladder, ovary, uterus, and bone.

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**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, small- and medium-sized follicles.

Epithelium lining follicles predominantly

flattened or low cuboidal.

Activity low.

Adrenal:

No alterations observed.

Moderate diffuse vacuolation of cells of zona

fasciculata.

Heart:

No alterations observed.

Slight chronic myocarditis.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

A large component of eosinophils present in

inflammatory response.

Spleen:

No alterations observed.

Minimal extramedullary hematopoietic activity.

Liver:

No alterations observed.

Many artifacts present making interpretation

difficult.

Slight nonsuppurative hepatitis.

Slight chronic pericholangitis.

Pancreas:

No alterations observed.

Slight chronic pancreatitis and focal acinar

atrophy.

GROUP NO. 1 Female Rat No. 82-708 (Continued)

GROSS

MICROSCOPIC

Mesenteric Lymph Node:

No alterations observed.

Activity appeared within normal limits.

Bone Marrow:

No alterations observed.

Small section included for examination.

Many megakaryocytes.

Maturing erythroid and myeloid cells seen in

moderate numbers.

Activity moderate.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, eye, kidney, stomach, small intestine, large intestine, urinary bladder, ovary, uterus, and bone.

GROSS Female Rat No. 82-709

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles chiefly flattened

or cuboidal in size.

Activity moderate.

Adrenal:

No alterations observed.

Slight vacuolation of cells in zona fasciculata.

Eve:

No alterations observed.

Section of optic nerve not included.

Lens shattered.

Otherwise, not remarkable.

Lung:

No alterations observed.

Moderate interstitial pneumonitis.

Moderate perivascular lymphoid hyperplasia.

Spleen:

No alterations observed.

Slight extramedullary hematopoietic activity.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Minimal chronic pericholangitis.

Kidney:

No alterations observed.

Rarely, a focus of chronic interstitial

nephritis.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared within normal limits.

## GROUP NO. 1 Female Rat No. 82-709 (Continued)

**GROSS** 

MICROSCOPIC

Ovary:

Left Ovary - Surrounded with

dark red cyst.

Not remarkable.

Cyst observed grossly not seen microscopically.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid

cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, stomach, pancreas, small intestine, large intestine, urinary bladder, uterus, and bone.

GROSS

MICROSCOPIC

Brain:

No alterations observed.

Minimal nonsuppurative meningocephalitis.

Slight focal gliosis.

Thyroid:

No alterations observed.

Medium- and large-sized follicles predominated.

Epithelium lining follicles chiefly flattened.

Activity very low.

Adrenal:

No alterations observed.

Moderate vacuolation of cells in zona fasciculata.

Eye:

No alterations observed.

Optic nerve section missing.

Center of lens missing.

Otherwise, not remarkable.

Heart:

No alterations observed.

Infrequent foci of chronic myocarditis.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Slight perivascular lymphocytic response.

Spleen:

Appeared enlarged.

Moderate extramedullary hematopoietic activity.

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Slight pericholangitis.

Kidney:

No alterations observed.

Rarely, a tiny focus of chronic interstitial

nephritis.

Minimal renal tubular regeneration.

## GROUP NO. 1 Female Rat No. 82-714 (Continued)

GROSS MICROSCOPIC

Pancreas:

No alterations observed.

Slight nonsuppurative pancreatitis with slight

ductal hyperplasia.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared to be within normal limits.

Ovary:

No alterations observed.

Activity appeared to be within normal limits.

Uterus:

Distended with clear

fluid.

Lumen distended.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid

cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: spinal cord, pituitary, stomach, small intestine, large intestine, urinary bladder, and bone.

GROSS Female Rat No. 82-726

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

MICROSCOPIC

Epithelium varied from a low cuboidal to a

plump cuboidal.

Activity moderately high.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal amount of pigment within red pulp.

Liver:

No alterations observed.

Minimal nonsuppurative hepatitis.

Uterus:

Distended with clear fluid.

Uterine lumen distended.

Otherwise, not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderate.

The follwoing organ was not altered grossly or microscopically: kidney.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles chiefly

flattened or low cuboidal in type.

Activity moderate.

Spleen:

Appeared enlarged.

Many artifacts from histologic preparation

makes interpretation difficult.

Slight extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Kidney:

Both pelves dilated.

Slight to moderate chronic interstitial

nephritis involving cortex and medulla.

Minimal regenerative tubular epithelial changes

associated with these inflammatory foci.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderate.

The following organ was not altered grossly or microscopically: liver.

GROSS Female Rat No. 82-729

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles chiefly flattened

or low cuboidal.

Activity low.

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic

activity.

Slight pigment within red pulp.

Kidney:

Dark red outer medulla.

Congestion in outer medulla.

Otherwise, not remarkable.

Bone Marrow:

No alterations observed.

Considerable numbers of megakaryocytes.

Considerable numbers of maturing erythroid and

myeloid cells.

Activity moderate.

The following organ was not altered grossly or microscopically: liver.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, medium- and large-sized follicles.

Epithelium lining the follicles flattened

or low cuboidal.

Activity low.

Lung:

Small, cyst-like areas.

Marked bronchial dilatation.

Moderate interstitial pneumonitis.

Minimal lymphocytic perivascular infiltration.

Spleen:

Appeared enlarged.

Moderate extramedullary hematopoietic activity.

Slight amount of pigment within red pulp.

Liver:

No alterations observed.

Slight extramedullary hematopoietic activity.

Minimal nonsuppurative hepatitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis involving

cortex and medulla.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderate.

GROSS Female Rat No. 82-73

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium chiefly flattened or low cuboidal

in type.

Activity low.

Spleen:

Appeared enlarged.

Some artifacts due to histologic preparation.

Slight to moderate extramedullary hemasspoietic

activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Slight pericholangitis.

Minimal nonsuppurative hepatitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis involving

cortex and medulla.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Medium- and large-sized follicles predominated.

Epithelium lining the follicles chiefly flattened

or low cuboidal.

Activity low.

Lung:

Median lobe consolidated.

Severe interstitial pneumonitis with wide-

spread consolidation of pulmonary parenchyma.

Moderately large peribronchial lymphocytic

aggregates.

One large area of pulmonary emphysema present.

Spleen:

No alterations observed.

Minimal extramedullary hematopoiati: activity

and minimal pigment within red pulp.

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Otherwise, not remarkable.

Kidney:

No alterations observed.

Very minimal chronic interstitial nephritis.

Bone Marrow:

No alterations observed.

Section too small and not adequate for evaluation;

however, activity appeared to be within normal

limits.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

One small focus of lymphocytic infiltration.

Epithelium lining the follicles flattened or

low cuboidal.

Activity judged to be low.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment in red pulp.

Liver:

No alterations observed.

Slight nonsuppurative hepatitis.

Kidney:

No alterations observed.

Slight chronic interstitial nephritis involving

medulla.

Small Intestine:

Duodenal lining thickened

and contained small, yellow

foci.

Not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles varied from

flattened to cuboidal.

Activity low.

Lung:

Dark red areas in all

lobes.

Rather large areas of pulmonary congestion and

edema as well as hemorrhage.

Slight to moderate interstitial pneumonitis.

Moderate perivascular lymphoid infiltration

present.

Slight alveolar emphysema.

Spleen:

No alterations observed.

Slight extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Bone Marrow:

No alterations observed.

Small section.

Many megakaryocytes present.

Many maturing erythroid and myeloid cells.

Activity moderate.

The following organs were not altered grossly or microscopically: liver and kidney.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly medium- and large-sized follicles.

Epithelium lining the follicles flattened or

low cuboidal, chiefly.

Activity judged to be low.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Slight pigment in red pulp.

Liver:

Yellowish tinge.

Infrequent foci of nonsuppurative hepatitis.

Otherwise, not remarkable.

Kidney:

No alterations observed.

Minimal tubular regeneration in cortex.

Small Intestine:

In duodenum; small, yellow

foci.

Walls appeared thickened.

Not remarkable.

Uterus:

Walls distended with clear

fluid.

Uterine lumen moderately distended.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles flattened or

low cuboidal in type.

Activity low.

Spleen:

No alterations observed.

Slight extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Kidney:

No alterations observed.

Very minimal chronic interstitial nephritis.

Bone Marrow:

No alterations observed.

Only a small section included for examination.

Marrow appeared well populated with erythroid

and myeloid cells and megakaryocytes.

Skin:

Severe alopecia on body.

Possibly, a slight hyperkeratosis.

Inflammatory changes not observed.

The following organ was not altered grossly or microscopically: liver.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles varied from

a flattened to plump cuboidal.

Activity moderate.

Pituitary:

No alterations observed.

Solitary cyst involving the pars distalis

containing eosinophilic secretory material

and calcareous bodies.

Heart:

No alterations observed.

Slight chronic myocarditis and epicarditis.

Lung:

Distended with abscessed

areas.

Severe bronchiectasis.

Bronchi wildly dilated and filled with purulent

exudate.

Dense zones of chronic inflammatory tissue

surrounding the effected bronchi.

Spleen:

No alterations observed.

Some tearing of tissues due to histologic

preparation.

Slight extramedullary hematopoietic activity.

Slight to moderate amounts of pigment in red

pulp.

### GROUP NO. 4 Female Rat No. 82-766 (Continued)

**GROSS** 

MICROSCOPIC

Liver:

Lobes thickened and pale

yellowish brown.

Slight pericholangitis.

In some areas, hepatocytes had vacuolated,

swollen cytoplasm.

Kidney:

Pale yellowish brown

cortex.

Dark red medulla.

Not remarkable.

Bone Marrow:

No alterations observed.

Numerous maturing erythroid and myeloid

cells.

Numerous megakaryocytes.

Activity moderately high.

Small Intestine:

Walls appeared thickened.

Entire circumference of the intestine not

included on this section.

Artifactual disruption of villi.

Vacuolation of cells in lamina propria.

The following organs were not altered grossly or microscopically: brain, spinal cord, adrenal, eye, stomach, pancreas, large intestine, urinary bladder, mesenteric lymph node, overy, uterus, and bone.

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining follicles chiefly flattened

or low cuboidal.

A few cystic follicles seen.

One cystic follicle filled with colloid the others

filled with cellular debris resembling

keratinaceous material.

Activity moderate.

Two large foci of lymphocytic infiltration.

Eye:

No alterations observed.

Artifacts present, otherwise, not remarkable.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Perivascular aggregates of lymphocytes and

plasma cells.

Spleen:

The second of th

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Liver:

No alterations observed.

Rare focus of nonsuppurative hepatitis.

Slight irregularity in cords of cells.

GROUP NO. 4 GROUP NO. 4
Female Rat No. 82-768 (Continued)
MICROSCOPIC

**GROSS** 

Stomach:

Walls appeared thickened.

Not remarkable.

Bone Marrow:

No alterations observed.

Many megakaryocytes.

Numerous maturing erythroid and myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, heart, kidney, pancreas, small intestine, large intestine, urinary bladder, mesenteric lymph node, ovary, uterus, and bone.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small- and medium-sized follicles predominated.

Epithelium lining the follicles chiefly

low cuboidal or cuboidal.

Activity moderate.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Slight perivascular aggregates of lymphocytes

and plasma cells.

Spleen:

No alterations observed.

Slight extramedullary hematopoietic activity.

Minimal pigment in red pulp.

Stomach:

Walls thickened.

Focal nonsuppurative gastritis seen with very

small numbers of chronic inflammatory cells

in submucosa.

Small Intestine:

Duodenum wall thickened

with small, yellow foci.

Not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Considerable numbers of maturing erythroid

and myeloid cells.

Activity moderately high.

# GROUP NO. 4 Female Rat No. 82-770 (Continued)

MICROSCOPIC

Skin:

Alopecia on body.

Section of skin preserved.

Not remarkable.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, eye, heart, liver, kidney, pancreas, large intestine, urinary bladder, mesenteric lymph node, ovary, uterus, and bone.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles either flattened

or low cuboidal in type.

Activity low.

Heart:

No alterations observed.

Minimal focal chronic myocarditis.

Lung:

Distended with consolidated

areas.

Minimal interstitial pneumonitis.

Slight perivascular and peribronchiolar lymphoid

infiltration.

Spleen:

Appeared slightly enlarged.

Moderate extramedullary hematopoietic activity.

Minimal pigment in red pulp.

Liver:

Yellowish tinge.

Slight nonsuppurative hepatitis.

Minimal chronic pericholangitis.

## GROUP NO. 4 Female Rat No. 82-771 (Continued)

GROSS MICROSCOPIC

Kidney:

Yellowish brown cortex.

Dark red outer medulla.

Moderate interstitial nephritis with

infiltrations of chronic inflammatory cells.

Inflammatory changes involved both cortex

and medulla.

Slight tubular dilatation and regenerative

tubular changes.

Small Intestine:

Lining of the duodenum

contained small, yellow

foci; walls appeared

thickened.

Not remarkable.

Urinary Bladder:

No alterations observed.

No section available for examination.

Mesenteric Lymph Node:

No alterations observed.

In the perinodal fat, a small focus of

chronic inflammation.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Considerable numbers of maturing erythroid and

myeloid cells.

Activity moderate to moderately high.

# GROUP NO. 4 Female Rat No. 82-771 (Continued)

GROSS

MICROSCOPIC

The follwoing organs were not altered grossly or microscopically: brain, spinal cord. pituitary, adrenal, eye, stomach, pancreas, large intestine, ovary, uterus, and bone.

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Epithelium lining the follicles cuboidal or

high cuboidal.

Activity moderate to moderately high.

Eye:

No alterations observed.

Staining artifacts present, otherwise, not

remarkable.

Lung:

No alterations observed.

Foci of chronic interstitial pneumonitis.

Small leukocytic cuffs evident around some

blood vessels.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Minimal pigment within red pulp.

Kidney:

No alterations observed.

Very minimal cast formation in some cortical

tubules.

Uterus:

Distended with clear

fluid.

Lumen slightly distended.

Mild dilatation of a few uterine glands.

## GROUP NO. 4 Female Rat No. 82-772 (Continued)

GROSS (Continued)

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Numerous maturing erythroid and myeloid cells.

MICROSCOPIC

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, adrenal, liver, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, ovary, and bone.

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Small-, medium-, and large-sized follicles.

Most follicles lined by cuboidal epithelium.

Minimal focal chronic thyroiditis and

fibrosis in association with cystic follicles.

Adrenal:

No alterations observed.

Only small section of medulla included.

Not remarkable.

Lung:

No alterations observed.

Minimal interstitial pneumonitis and

lymphoid hyperplasia.

Streen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Moderate amount of golden brown pigment

within red pulp.

Liver:

No alterations observed.

Poor histologic section.

Otherwise, not remarkable.

# GROUP NO. 5 Female Rat No. 82-786 (Continued)

GROSS

MICROSCOPIC

#### Kidney:

Pelvis dilated and contained small, firm, sandlike granules.

Severe pyelonephritis with ulceration of the epithelium lining the renal pelvis.

Renal pelvis and adjacent medulla are diffusely infiltrated with chronic inflammatory cells.

Many polymorphs infiltrate the pelvic mucosa.

Tubules in affected areas wildly separated by inflammatory exudate.

Occasional tubules have small numbers of neutrophils in their lumens.

Cortex only minimally effected.

#### Urinary Bladder:

Walls thickened, dark pink, and rough.

Contained numerous, firm, white stones measuring approximately 1 x 0.5 cm. to small granules.

Mucosa greatly thickened and thrown up into tortuous folds.

Within lamina propria collections of acute and chronic inflammatory cells, including plasma cells.

## GROUP NO. 5 Female Rat No. 82-786 (Continued)

**GROSS** 

MICROSCOPIC

Edematous separation of the muscle layers and infiltrations of chronic inflammatory cells and pigment containing macrophages.

Histopathologic changes correspond to a moderately severe, chronic hyperplastic cystitis.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared to be within normal limits.

Ovary:

No alterations observed.

Activity appeared to be within normal limits.

Bone Marrow:

No alterations observed.

Moderately high numbers of megakaryocytes.

Considerable numbers of maturing erythroid and myeloid elements.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, eye, heart, stomach, pancreas, small intestine, large intestine, uterus, and bone.

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Chiefly, medium- and large-sized follicles.

Follicles lined by flattened or low cuboidal

epithelium.

Activity low.

Adrenal:

No alterations observed.

Adrenal medulla not included for examination.

Moderately high vacuolation of cells in zona

fasciculata.

Eye:

No alterations observed.

Lenses shattered and displaced.

Section does not include optic nerve.

Otherwise, not remarkable.

Lung:

No alterations observed.

Slight interstitial pneumonitis.

Minimal peribronchial lymphoid hyperplasia.

Spleen:

Appeared enlarged.

Slight extramedullary hematopoietic activity.

Liver:

No alterations observed.

Slight chronic pericholangitis.

Kidney:

No alterations observed.

Minimal chronic interstitial nephritis.

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GROSS \_\_\_\_

MICROSCOPIC

Pancreas:

No alterations observed.

Minimal chronic pancreatitis.

Large Intestine:

No alterations observed.

Lumen distended.

Otherwise, not remarkable.

Mesenteric Lymph Node:

No alterations observed.

Small section represented.

Activity appeared within normal limits.

Ovary:

No alterations observed.

Activity appeared within normal limits.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Considerable numbers of maturing erythroid and

myeloid cells.

Activity moderate.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, stomach, small intestine, urinary bladder, uterus, and bone.

### GROUP NO. 5 Female Rat No. 82-792

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Chieffy, small- and medium-sized follicles.

Epithelium lining follicles flattened to

cuboidal.

Activity moderate.

Adrenal:

No alterations observed.

Moderately high degree of vacuolation of cells

in zona fasciculata.

Eye:

No alterations observed.

Optic nerve not represented on section.

Otherwise, not remarkable.

Lung:

Abscessed areas.

Moderate interstitial pneumonitis and moderate

lymphoid peribronchial hyperplasia.

Areas of bronchiectasis also seen.

Spleen:

No alterations observed.

Slight to moderate extramedullary hematopoietic

activity.

Pigment minimal in red pulp.

Liver:

No alterations observed.

Minimal focal areas of necrosis seen with

a mononuclear inflammatory cell infiltration.

## GROUP NO. 5 Female Rat No. 82-792 (Continued)

GROSS

MICROSCOPIC

Kidney:

No alterations observed.

A very few foci of chronic interstitial

nephritis associated with infrequent

tubules showing regenerative changes.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared to be within normal limits.

Uterus:

No alterations observed.

Lumen appeared slightly distended.

Otherwise, not remarkable.

Bone Marrow:

No alterations observed.

Numerous megakaryocytes.

Considerable numbers of maturing erythroid and

myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, stomach, pancreas, small intestine, large intestine, urinary bladder, ovary, and bone.

# GROUP NO. 5 Female Rat No. 82-793

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Medium- and large-sized follicles predominated.

Epithelium lining follicles a flattened or

low cuboidal type.

Activity low.

Adrenal:

No alterations observed.

Low level of vacuolation of cells in zona

fasciculata.

Eye:

No alterations observed.

Anterior segments missing including cornea,

iris, and ciliary processes.

Lenses shattered and displaced.

Section does not include optic nerve.

Retina and coroid, not remarkable.

Heart:

No alterations observed.

Minimal nonsuppurative myocarditis.

Lung:

No alterations observed.

Moderate interstitial pneumonitis and

moderate peribronchial lymphoid hyperplasia.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Liver:

No alterations observed.

Infrequent foci of mononuclear cell infiltration

seen.

## GROUP NO. 5 Female Rat No. 82-793 (Continued)

GROSS MICROSCOPIC

Kidney:

No alterations observed.

Infrequent foci of chronic interstitial

nephritis.

Minimal areas of regenerating tubular

epithelium in cortex.

Mesenteric Lymph Node:

No alterations observed.

Activity appeared within normal limits.

Uterus:

Distended with clear

fluid.

Lumens distended.

Mild cystic endometrial hyperplasia.

Bone Marrow:

No alterations observed.

Moderate numbers of megakaryocytes.

Considerable numbers of maturing erythroid

and myeloid cells.

Moderately high activity.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, stomach, pancreas, small intestine, large intestine, urinary bladder, ovary, and bone.

GROUP NO. 5
Female Rat No. 82-795

GROSS

MICROSCOPIC

Pituitary:

No alterations observed.

Only pars distalis represented on the section.

Otherwise, not remarkable.

Thyroid:

No alterations observed.

Section not available for examination.

Adrenal:

No alterations observed.

Moderate degree of vacuolation of cells in

zona fasciculata.

Lung:

No alterations observed.

Moderate interstitial pneumonitis and

peribronchial lymphoid hyperplasia.

Spleen:

No alterations observed.

Moderate extramedullary hematopoietic activity.

Liver:

Mottled surface.

Slight chronic pericholangitis.

Kidney:

No alterations observed.

Occasional small foci of chronic interstitial

nephritis.

A few tubules in medulla distended.

One dilated tubule surrounded by amorphous

pink material.

Pancreas:

No alterations observed.

One dilated pancreatic duct surrounded by

a small zone of chronic inflammation.

GROUP NO. 5
Female Rat No. 82-795 (Continued)

GROSS

MICROSCOPIC

Ovary:

No alterations observed.

Activity appeared within normal limits.

Uterus:

No alterations observed.

Slight cystic endometritis.

Bone Marrow:

No alterations observed.

Considerable numbers of megakaryocytes.

Considerable numbers of maturing erythroid and

myeloid cells.

Activity moderately high.

The following organs were not altered grossly or microscopically: brain, spinal cord, eye, heart, stomach, small intestine, large intestine, urinary bladder, mesenteric lymph node, and bone.

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#### SUMMARY

One hundred healthy albino rats of the Charles River Caesarean-derived strain (50 males and 50 females) were divided by stratified randomization into five groups of 10 males and 10 females each. Group No. 1 served as the vehicle control. Groups No. 2, No. 3, No. 4, and No. 5 received the test compound, WR-2823 (AU 69115), via intravenous injection at the rates of 30, 60, 120, and 15 mg/kg/day, respectively, administered in a vehicle of 0.9% sterile saline. The first five rats in each group received 16 injections, and the last five in each group received 15 injections. Rats were killed on the day following the last dose. The following tissues were collected in 10% buffered formalin from Group No. 1 (control), Group No. 5 (low level), and Group No. 4 (high level) and examined microscopically: brain, pituitary, eye, spinal cord (three levels), thyroid, lung, heart, spleen, liver, kidney, adrenal, stomach, pancreas, small intestine, large intestine, urinary bladder, mesenteric lymph node, testis, ovary, prostate, uterus, bone marrow, bone, and unusual lesions. Eyes were fixed in alcoholic formalin. From male and female rats in Groups No. 2 and No. 3, sections of thyroid, liver, spleen, kidney, and unusual lesions were examined.

Definite, compound-related changes were not observed in this study.

Rare histopathologic findings in the treated groups consisted of: dacryoadenitis, focal thyroiditis, gastritis (two animals), pyelonephritis, prostatitis,
and severe chronic cystitis in one Group No. 5 rat (low level). Sections of
spinal cord, pituitary, and eye were unremarkable from the treated groups. The
histologic appearance of the pituitary, adrenal, spleen, mesenteric lymph node,
and bone marrow were comparable between the control and treated rats.

Histopathologic findings which were comparable in incidence and severity in control and treated animals included: chronic interstitial nephritis, pyelitis, chronic nonsuppurative meningoencephalitis, myocarditis and epicarditis, chronic murine pneumonia complex, nonsuppurative hepatitis and pericholangitis, nonsuppurative pancreatitis, and mild nonsuppurative cystitis.

Sections of pituitary, eye, stomach, and prostate from control animals were not considered remarkable. Other histopathologic changes listed in the incidence table or mentioned in the detailed pathology section and not mentioned in this summary are considered incidental findings not related to the compound administration.

In summary, the intravenous injection of the compound, WR-2823 (AU 69115), at levels of 15, 30, 60, and 120 mg/kg/day for two weeks did not produce compound-related, histopathologic changes in any of the tissues examined.

### KEY TO DETAILED HISTOPATHOLOGY INCIDENCE TABLE

N = No Section

X = Not Remarkable

A = Autolysis

P or √ = Present or Taken

0 = Absent

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderate to Severe

5 = Severe

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### DETAILED HISTOPATHOLOGY INCIDENCE TABLE

	MALES GROUP NUMBER													
		1					GROUF NUMBER							
KAL G G	96	8	,02	.03	70,		16	71	18	19	21			
ORGANS	82-696	82-700	82-702	82~703	82-704		82-716	82-717	82-718	82-719	82-721			
BRAIN Nonsuppurative Meningitis Perivascular Cuffing Glial Nodules Meningoencephalitis	P 2	x	2 P 2	P 2	2									
SPINAL CORD Focal Gliosis Nonsuppurative Meningitis Meningomyelitis	P	X	P	X	X									
PITUITARY	x		X	X	x									
THYROID Level of Activity	3	4	3	3	2		2	2	2	4	2			
EYE Dacryoadenitis Myositis	x	X	X	X	2									
HEART Epicarditis Focal Myocarditis Endocarditis	1	2 3 3	2 2 2	2 2	1									
LUNG Bronchiectasis Emphysema Interstitial Pneumonitis Peribronchial Lymphoid Hyperplasia	2	2	3 2	2	2 2			3	3					
SPLEEN Extramedullary Hematopoiesis	2	2	2-3	2-3	3-4	;	2-3	2	2-3	4	3			
LIVER Nonsuppurative Hepatitis Necrosis Pericholangitis	2	2	2	2	2		1	2	1	2	x			
KIDNEY Interstitial Nephritis Pyelitis Regenerative Epithelium	2 2	x	2 2 2	2	2		x	2	3 2 2-3	3				

#### HAZLETON LABORATORIES, INC.

TAW LIFE SCIENCES CENTER

Sponsor:

Walter Reed Army Institute of Research

Date:

September 28, 1970

Material:

WR-2823 (AU 69115)

Subject:

REPORT NO. 37

Pathology Report

Two-Week Intravenous Toxicity Study - Dogs

Project No. 193-411

This pathology report is a supplement to Report No. 29 dated, January 14, 1970, entitled "Two-Week Intravenous Toxicity Study - Dogs" on compound, WR-2823 (AU 69115). In that report the results were reported without the histopathologic evaluation of tissues.

Submitted by

FOR MARCELINA B. POWERS, D.V.M., M.S.

Director, Drugs and

Industrial Chemicals Department Toxicology-Biosciences Laboratory

Pathology by

Staff Pathologist

saw

# HISTOPATHOLOGICAL EVALUATION FOR MALE AND FEMALE BEAGLE DOGS SACRIFICED AT TERMINATION

GROUP NO. 1 Male Dog No. 14121

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Moderate- to large-sized follicles predominated.

Follicles lined by low cuboidal or flattened

epithelium.

Activity judged moderate by microscopic

appearance.

Spleen:

No alterations observed.

A few megakaryocytes scattered throughout red

pulp.

Small amount of brown, granular pigment in red

pulp.

Urinary Bladder:

No alterations observed.

One small area of ulceration infiltrated by

polymorphonuclear leukocytes and hemorrhage.

Inflammatory response spreads only a short

distance into the submucosa.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, eye, heart, lung, gallbladder, liver, kidney, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, prostate, testis with epididymis, nerve with muscle, and rib (bone).

### GROUP NO. 1 Male Dog No. 14125

**GROSS** MICROSCOPIC Thyroid: No alterations observed. Moderate- to large-sized follicles predominated. Follicles lined by low cuboidal or flattened epithelium. Follicular epithelium moderate in amount. Activity judged to be moderate based on microscopic appearances. Adrenal: No alterations observed. Cells of the zona fasciculata diffusely vacuolated. Kidney: No alterations observed. Occasional glomeruli in which the glomerular tuft was shrunken and a pink, amorphous sediment existed within the glomerular space along with small quantities of brown pigment. Prostate: No alterations observed. In one area, a focus of lymphocytic infiltration.

Section missing.

Nerve with Muscle:

No alterations observed.

### GROUP NO. 1 Male Dog No. 14125 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Complete maturation of erythroid and myeloid elements.

Low number of megakaryocytes.

Small amounts of pigment within macrophages.

Activity low.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, eye, heart, lung, gallbladder, liver, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testis with epididymis, and bone.

### GROUP NO. 2 Male Dog No. 14251

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Follicles predominantly large or medium size.

Colloid brightly eosinophilic.

Follicles lined by flattened or low cuboidal

epithelium.

Activity judged to be low by histologic criteria.

Spleen:

No alterations observed.

Lymphoid follicles appeared normal.

Greater abundance of red pulp than white pulp.

Megakaryocytes rare.

Pigment within red pulp present in very low

quantities.

Kidney:

No alterations observed.

Minimal, very infrequent areas of chronic

interstitial nephritis, tubular regeneration,

and tubular dilatation.

Urinary Bladder:

Contains single, hemorrhagic-

appearing area.

Slight acute inflammatory changes with hemorrhage,

edema, and infiltrations of polymorphonuclear

leukocytes.

A few arterioles in the submucosa had fibrinoid

changes.

### GROUP NO. 2 Male Dog No. 14251 (Continued)

GROSS MICROSCOPIC

Bone Marrow:

No alterations observed.

Complete maturation of erythroid and myeloid

elements.

Megakaryocytes few in number.

Small amount of pigment in red pulp.

Activity judged to be low.

The following organs were not altered grossly or microscopically: liver and pancreas.

### GROUP NO. 2 Male Dog No. 14253

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Medium- and large-sized follicles.

Colloid brightly eosinophilic.

Follicles lined by flattened or low cuboidal

epithelium.

Activity judged to be low.

Spleen:

No alterations observed.

Proportion of reticuloendothelial tissue to

lymphoid tissue, high.

Megakaryocytes infrequent.

Pigment within red pulp very low.

Liver:

No alterations observed.

Many hepatocytes, often swollen with a vacuolated

cytoplasm.

Kidney:

No alterations observed.

Few glomeruli had shrunken glomerular tufts with

the presence of pink, proteinaceous exudate

within the glomerular space.

Bone Marrow:

No alterations observed.

Hematopoietic cells very scarce.

Section composed mainly of fat.

Minimal numbers of megakaryocytes.

### GROUP NO. 2 Male Dog No. 14253 (Continued)

GROSS

MICROSCOPIC

Erythroid and myeloid cell maturation complete.

Amount of pigment within bone marrow very low.

Activity of marrow appeared low.

The following organ was not altered grossly or microscopically: urinary bladder.

### GROUP NO. 3 Male Dog No. 14366

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Thyroid follicles predominantly medium to large

in size.

Colloid brightly eosinophilic.

Follicles lined by flattened or low cuboidal

epithelium.

Overall activity of thyroid judged to be low.

Spleen:

No alterations observed.

Lymphoid follicles appeared normal with a

preponderance of immature lymphocytic cells.

Ratio of reticuloendothelial tissue to lymphoid

tissue, high.

Kidney:

No alterations observed.

Minimal small foci of chronic interstitial

nephritis at corticomedullary junction.

Bone Marrow:

No alterations observed.

Erythroid and myeloid maturation appeared

complete.

Very few megakaryocytes present.

Presence of hemosiderin pigment very low.

Overall activity of the marrow low.

The following organs were not altered grossly or microscopically: liver, urinary bladder, and pancreas.

### GROUP NO. 3 Male Dog No. 14389

**GROSS** MICROSCOPIC Thyroid: No alterations observed. Large- and medium-sized follicles predominated. Colloid brightly eosinophilic. Thyroid follicles lined by flattened or low cuboidal epithelium. Overall activity of thyroid judged to be low. Gallbaldder: Moderately distended. Very few lymphoid follicles found in submucosa. Spleen: No alterations observed. Lymphoid follicles appeared normal. Quantity of reticuloendothelial tissue to lymphoid tissue, high. Minimal pigment within red pulp. Kidney:

Capsules appeared slightly

rough.

Medulla reddened.

Moderate changes primarily involving the cortex and consisting of focal areas of tubular dilatation; chronic interstitial nephritis; and tubular regeneration. Only occasionally did the dilated tubules contain any material. Small amounts of eosinophilic proteinaceous

sediment were seen in some tubules.

## GROUP NO. 3 Male Dog No. 14389 (Continued)

GROSS

#### MICROSCOPIC

Dilated tubules lined by flattened or low cuboidal epithelium.

Sparse infiltration by chronic inflammatory cells.

Tubular regeneration and dilated tubules most conspicous features.

Often in regenerating tubules, intracytoplasmic brown, granular pigment.

Similar pigment found in some unaffected convoluted tubules.

#### Pancreas:

No alterations observed.

Minimal chronic interstitial pancreatitis.

Urinary Bladder:

Mucosal surface appeared

hemorrhagic.

Mucosal epithelium absent in some areas.

In focal areas, mucosal epithelium appeared vacuolated, and small numbers of polymorphs infiltrated the epithelium.

Within the submucosa, infiltrations by polymorphs and lymphocytic cells.

Submucosal vessels markedly congested with small areas of hemorrhage in submucosa.

Histologic changes correspond to a subacute cystitis.

## GROUP NO. 3 Male Dog No. 14389 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Erythroid and myeloid cell maturation appeared

complete.

Moderate numbers of megakaryocytes.

Minimal pigment.

Activity low.

The following organ was not altered grossly or microscopically: liver.

## GROUP NO. 4 Male Dog No. 14494

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Follicles of moderate size predominated.

Follicles lined by low cuboidal or flattened

epithelium.

Thyroid activity on the basis of histologic

criteria judged to be low.

Gallbaldder:

No alterations observed.

A few lymphocytic aggregates in submucosa.

Spleen:

No alterations observed.

Lymphoid follicles appeared normal.

Lymphoid follicles had a predominance of

immature lymphocytic cells.

In a few cases, lymphoid follicles replaced by

an acellular, and homogeneous eosinophilic

material.

Liver:

Markedly distended (three

times normal).

Centrilobular congestion noted.

Cells in centrilobular portions of the lobules

had a decreased staining intensity.

Cord-like arrangement of hepatocytes in

centrilobular areas slightly disorganized.

## GROUP NO. 4 Male Dog No. 14494 (Continued)

GROSS

MICROSCOPIC

### Kidney:

Capsular surface covered with what appeared to be gray, pitted areas.

Irregularities in capsular surface characterized by small depressions.

Moderately great numbers of dilated tubules.

Dilated tubules often empty or contained a

small quantity of pale-staining eosinophilic

material.

Slight inflammatory cell infiltration.

Moderately large numbers of regenerating tubules.

Numerous tubules in cortex both within and outside these areas of hypercellularity contained intracytoplasmic, brown, granular pigment.

Glomeruli, chiefly in affected areas, appeared to show a thickening of basment membrane of glomerular tufts.

Rarely, mineralized tubules in the medulla.

#### GROUP NO. 4 Male Dog No. 14494

**GROSS** 

MICROSCOPIC

Adrenal:

No alterations observed.

Activity within normal limits.

Eye:

No alterations observed.

Slight acute conjunctivitis.

Slight acute superficial keratitis.

The inflammatory process extends only a short

distance from the limbus margin.

Heart:

No alterations observed.

In the epicardium near the larger coronary

vessels, there was an area of acute inflammation

chiefly within the fatty layer.

The inflammatory process also extended a short

distance into the myocardium.

Involvement of the myocardium minimal.

Pancreas:

No alterations observed.

Discrete interstitial alterations.

Histologic changes, in most cases, involved the

interlobular interstitial areas of acinar

pancreas with small nests and bands of elongated

cells which often contained a single discrete

cytoplasmic vacuole.

The type of cell showing these vacuolar changes

could not be identified with certainty.

In some cases, the vacuolated cells appeared to be

exocrine cells or ductular cells.

Inflammatory cells not observed.

## GROUP NO. 4 Male Dog No. 14494 (Continued)

GROSS

MICROSCOPIC

Urinary Bladder:

Walls slightly thickened

and the mucosa appeared

hemorrhagic.

Acute cystitis.

Focal vacuolation of the mucosal epithelial

cells.

Infiltration of polymorphonuclear leukocytes

into the mucosal epithelium.

Focal infiltration of polymorphonuclear

leukocytes into the submucosa and small

areas of hemorrhage.

Submucosal vessels congested.

Prostate:

No alterations observed.

Minimal acute prostatitis with infiltrations of

polymorphs in the interstitium and in the

capsule.

Collections of purulent exudate in the lumen of

some prostatic gland.

Testis:

No alterations observed.

Slight testicular degeneration, with the presence

in seminiferous tubules of giant cells and

other abnormal forms.

## GROUP NO. 4 Male Dog No. 14494 (Continued)

**GROSS** 

MICROSCOPIC

Nuclei of some spermatogonia very large and vacuolated.

In the head of the epididymis, there was pronounced vacuolar change of the epithelial cells lining the epididymal duct.

To a marked degree, there was phagocytosis of spermatozoal precursor cells by the epididymal duct epithelium.

Bone Marrow:

No alterations observed.

Normal maturation of erythroid and myeloid elements.

Megakaryocytes in small numbers.

Activity judged to be moderate.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, lung, stomach, small intestine, large intestine, mesenteric lymph node, nerve with muscle, and rib (bone).

### GROUP NO. 4 Male Dog No. 14502

**GROSS** 

MICROSCOPIC

Thyroid:

Right thyroid 2 x 3 mm.; cyst-

like formations on anterior

end.

Thyroid follicles moderate or large in size.

Follicles at periphery of thyroid gland

distended with colloid and probably represent

cyst-like formations seen grossly.

Parafollicular tissue moderate in amount.

Thyroid follicles lined by low cuboidal or

flattened epithelium.

Activity low.

Gallbladder:

Distended approximately two

times normal size.

Few lymphoid follicles in submucosa.

Spleen:

No alterations observed.

Lymphoid follicles relatively large with

moderate numbers of mitotic figures evident

within their centers.

Immature lymphocytic cell predominated.

Minimal pigment within macrophages of red pulp.

Megakaryocytes infrequently observed.

Liver:

No alterations observed.

At peripheral portions of the lobule, liver

cells vacuolated and slightly swollen.

Pigment within Kupffer cells minimal.

### GROUP NO. 4 Male Dog No. 14502 (Continued)

**GROSS** 

MICROSCOPIC

Kidney:

Capsule white and pitted.

Medulla and hilus of

kidney reddened.

Linear streaks of hypercellularity in cortex.

Moderate numbers of lymphocytic cells and few plasma cells infiltrated affected areas.

Many tubules in affected areas closely packed, small with increased basophilic.

Moderate regenerative changes.

Moderate numbers of tubules in areas dilated and contained small amount of pink, protein-aceous sediment.

Tubules both within and outside affected areas contained small, brown, granules of intracytoplasmic pigment.

Moderate numbers of glomeruli showed thickening of the basment membrane of the tuft as well as the basement membrane of Bowman's capsule.

Fibrosis minimal.

Medulla rarely involved, but small areas of inflammatory cell infiltration and regenerative tubules occasionally seen in outer medulla.

Rarely, mineralized tubules in medulla.

Rarely, polymorphs within a few dilated tubules.

## GROUP NO. 4 Male Dog No. 14502 (Continued)

GROSS |

Adrenal:

No alterations observed.

Activity within normal limits.

Prostate:

No alterations observed.

Moderate suppurative prostatitis with purulent

MICROSCOPIC

exudate in many glandular lumens.

Affected tubules surrounded by small numbers

of acute and chronic inflammatory cells.

Urinary Bladder:

Walls thickened.

Mucosal surface hemorrhagic.

Bladder mucosa varied markedly in thickness.

Bladder mucosa completely denuded in some

areas.

Mucosal epithelium rather generally infiltrated

with neutrophils, with focal epithelial

vacuolation.

Within the submucosa many large areas of

hemorrhage, infiltrations of polymorphs, and

mononuclear inflammatory cells.

Basal layers of the submucosa quite edematous.

Mild leukocytic infiltration also seen within

superficial muscle layers.

Testis:

Odd, brown tinge evident

grossly.

Moderately large numbers of spermatozoe in

epididymal ducts.

## GROUP NO. 4 Male Dog No. 14502 (Continued)

**GROSS** 

MICROSCOPIC

Seminiferous tubules exhibited a moderate

to high level of activity.

Bone Marrow:

No alterations observed.

Myeloid and erythroid maturation complete.

Megakaryocytes few in numbers.

Overall activity judged to be slight.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, eye, heart, lung, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, nerve with muscle, and rib (bone).

### GROUP NO. 5 Male Dog No. 14504

**GROSS** MICROSCOPIC Brain: No alterations observed. Mild autolysis. Pituitary: No alterations observed. Autolytic changes evident with individualization of cells in pars distalis. Thyroid: Many large- and medium-sized follicles. Enlarged. Colloid richly eosinophilic. Epithelial cells lining follicles predominantely low cuboidal or cuboidal. Desquamation of some follicular epithelial cells into the centers of thyroid follicles, and probably represented an artifact. Activity low. Adrenal: Autolytic changes, especially in adrenal medulla. No alterations observed. Occasional foci of cellular vacuolation in zona glomerulosa. Cells within the zona fasciculata appeared rather uniformly vacuolated. Eye: No alterations observed. Poor histologic preparation.

Cornea folded.

## GROUP NO. 5 Male Dog No. 14504 (Continued)

GROSS

MICROSCOPIC

Retina detached and choroid disrupted.

Retina showed evidence of postmortem autolysis.

Mild chronic conjunctivitis of palpebral

conjunctiva.

Lung:

No alterations observed.

Pronounced congestion.

Significant autolytic changes.

Gallbladder:

No alterations observed.

Advanced autolysis.

Impossible to evaluate histologically.

Spleen:

Enlarged.

Advanced autolysis.

A critical histopathologic evaluation

impossible.

Liver:

Enlarged.

Areas of autolysis present.

Marked congestion.

Much acid hematin pigment distributed throughout

liver tissue.

Kidney:

No alterations observed.

Autolytic changes present which made critical

evaluation impossible.

Cortex and medulla markedly congested.

## GROUP NO. 5 Male Dog No. 14504 (Continued)

**GROSS** 

MICROSCOPIC

Epithelium lining renal pelvis quite vacuolated and infiltrated by small numbers of polymorphs.

Stomach:

No alterations observed.

Autolytic changes.

Small Intestine:

No alterations observed.

Extensive autolysis.

Large Intestine:

No alterations observed.

Extensive autolysis.

Mesenteric Lymph Node:

No alterations observed.

Autolytic changes.

Urinary Bladder:

No alterations observed.

Much of the mucosal epithelium had undergone postmortem desquamation; otherwise, not

remarkable.

Inflammatory changes not evident in submucosa.

Prostate:

No alterations observed.

Poor cytological detail due to postmortem

autolytic changes.

Testis:

No alterations observed.

Normal spermatozoa formation.

Spermatozoa present within epididymal ducts.

Overall spermatozoa formation judged to be

low.

# GROUP NO. 5 Male Dog No. 14504 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Many artifacts of histologic preparation.

Poor cytologic detail prevents an adequate

appraisal of hematogenic activity.

The following organs were not altered grossly or microscopically: heart, pancreas, nerve with muscle, and bone.

### GROUP NO. 5 Male Dog No. 14515

GROSS |

Thyroid:

No alterations observed.

Follicles predominantly large or medium size.

MICROSCOPIC

Colloid brightly eosinophilic.

Follicles for the most part lined by flattened

or low cuboidal epithelium.

Parafollicular tissue very scant in amount.

Adrenal:

No alterations observed.

Cells of the zona fasciculata rather

uniformly and finely vacuolated.

Eye:

No alterations observed.

Many artifacts (folded cornea, shattered lens,

detached retina, and disrupted choroid).

Otherwise, histologic appearance not

remarkable.

Gallbladder:

No alterations observed.

Autolytic changes present.

Spleen:

Enlarged.

Collections of polymorphs generally distributed

throughout red pulp.

Autolytic changes make interperation difficult.

Liver:

No alterations observed.

Congestion.

Focal hepatic cell vacuolation.

## GROUP NO. 5 Male Dog No. 14515 (Continued)

GROSS	MICROSCOPIC
Kidney:	
No alterations observed.	Great numbers of dilated tubules in cortex and
	medulla.
	Tubules essentially devoid of any sediment or
	foreign material, but a few contained small
	amount of eosinophilic, granular sediment.
	Affected tubules appeared to be mainly distal
	convoluted tubules and collecting tubules.
	Dilated tubules lined by an intact epithelial
	layer, which is attenuated.
	Proteinaceous cast present in small numbers in
	collecting tubules near the renal papilla.
	A few recent soft thrombi seen in veins in the
	medulla.
	Only infrequent foci of chronic inflammatory
	cells were seen in the cortex.
Stomach:	
No alterations observed.	Section not present.
Small Intestine:	
No alterations observed.	Autolysis of the superficial mucosa.
Prostate:	

No alterations observed. Section missing.

## GROUP NO. 5 Male Dog No. 14515 (Continued)

GROSS

MICROSCOPIC

Testis:

No alterations observed.

Spermatogenic activity very low.

Very low number of mature spermatozoa within

epididymis.

Spermatozoal precursors found within some

epididymal ducts.

It was possible that the dog was just approaching

sexual maturity.

Bone Marrow:

No alterations observed.

Complete maturation of erythroid and

myeloid cells.

Megakaryocytes present in low numbers.

Very low amount of pigment present.

Overall activity of the marrow judged to be

moderate.

The following organs were not altered grossly or microscopically: brain, pituitary, heart, lung, pancreas, large intestine, mesenteric lymph node, urinary bladder, nerve with muscle, and bone.

### GROUP NO. 1 Female Dog No. 14333

GROSS	MICROSCOPIC
Brain:	
No alterations observed.	At the level of the pons, one capillary in the
	white matter cuffed by a small number of
	lymphocytes and microglial cells; not a
	significant alteration.
Thyroid:	
No alterations observed.	A predominance of moderate-sized follicles.
	Follicles lined for the most part by a low
	cuboidal or flattened epithelium.
	Moderate parafollicular tissue.
	Overall activity judged to be low.
Adrenal:	
No alterations observed.	Moderate vacuolation of cells in zona
	fasciculata.
Spleen:	
No alterations observed.	A tip of splenic parenchyma exhibited postmortem
	autolysis.
	Lymphoid follicles of normal size and
	distrubition with a predominance of immature
	forms present.
	Megakaryocytes seen rarely.
	Adjacent to one of the large arteriers in the

splenic trabeculum; loosening of the smooth

#### GROUP NO. 1 Female Dog No. 14333 (Continued)

GROSS MICROSCOPIC

muscle fibers, with concommitant hemorrhage and,

deposition of hemosiderin pigment.

Hemosiderin pigment rarely seen in red pulp.

Liver:

No alterations observed. Slip

Slight vacuolation of hepatocytes near

periportal areas.

Pancreas:

No alterations observed.

Minimal focal chronic pancreatitis.

Small Intestine:

No alterations observed.

A few glands cystic-filled with a muscious-

appearing substance, a few desquamated

epithelial cells, and a few leukocytes.

Urinary Bladder:

No alterations observed.

The mucosal epithelium intact and regular in

thickness.

Polymorphs rather generally infiltrated the

mucosal epithelium.

Focal areas of hemorrhage into the mucosal

epithelium.

Submucosa congested, edematous in places, and

rather diffusely infiltrated with, mononuclear

inflammatory cells, and polymorphs.

Changes corresponded to an acute cystitis of

moderate degree.

# GROUP NO. 1 Female Dog No. 14333 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Erythroid maturation of cells complete.

Moderately high numbers of meagkaryocytes.

Quantity of pigment very low.

Hematogenic activity moderately high.

The following organs were not altered grossly or microscopically: pituitary, eye, heart, lung, gallbladder, kidney, stomach, large intestine, mesenteric lymph node, uterus, ovary, nerve with muscle, and bone.

#### GROUP NO. 1 Female Dog No. 14348

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Majority of thyroid follicles large and medium size and lined by flattened or low cuboidal epithelium.

Numerous parafollicular cells.

Overall activity of thyroid judged to be low.

Adrenal:

No alterations observed.

Moderate vacuolation of cells within the zona

fasciculata.

Eye:

No alterations observed.

Poor histologic preparation.

Cornes markedly folded and retins detached.

Choroid disrupted in some places.

Intraocular structures were poorly fixed, infiltrated, and impossible to evaluate critically.

Lung:

No alterations observed.

A few areas of alveolar thickening in focal locations by lymphocytes, erythrocytes, and a few polymorphs.

#### GROUP NO. 1 Female Dog No. 14348 (Continued)

GROSS	MICROSCOPIC
Spleen:	
No alterations observed.	Splenic follicles normal in size and distribution
	Megakaryocytes infrequent.
	Minimal pigment within macrophages of red pulp.
Liver:	
No alterations observed.	Many hepatocytes slightly swollen and vacuolated.
	Very small foci of leukocytic infiltration in
	periportal areas.
Kidney:	
No alterations observed.	Infrequent glomeruli were sclerotic and
	surrounded by a small rim of chronic
	inflammatory cells.
Urinary Bladder:	
No alterations observed.	Tissue poorly stained, probably the result
	of poor fixation.
	Areas of cystitis not seen.
Uterus:	
No alterations observed.	Section poorly stained.
	Otherwise, not remarkable.
Ovary:	

Section poorly stained.

No alterations observed.

## GROUP NO. 1 Female Dog No. 14348 (Continued)

**GROSS** 

MICROSCOPIC

Bone Marrow:

No alterations observed.

Myeloid and erythrocytic maturation complete.

Megakaryocytes relatively numerous.

Activity moderate.

Minimal pigment present in red pulp.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, heart, gallbladder, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, nerve with muscle, and bone.

#### GROUP NO. 2 Female Dog No. 14355

GROSS

MICROSCOPIC

Pituitary:

Small cyst in base.

One large cyst and a few smaller cysts involving the pars anterior.

The larger cysts filled by fine, fibrillar, eosinophilic material, with occasional globules, and cysts lined by flattened or columnar epithelium.

Some of the columnar cells resemble goblet cells, and had a brush border.

Thyroid:

No alterations observed.

Medium-sized with large-sized follicles predominated.

Colloid brightly eosinophilic.

Follicles lined by flattened or low cuboidal

epithelium.

Functional activity of the thyroid appeared to

be low.

Spleen:

No alterations observed.

Lymphoid follicles appeared normal.

Proportion of reticuloendothelial tissue to

lymphoid tissue, high.

Megakaryocytes infrequent.

Occasional pigment within red pulp.

# GROUP NO. 2 Female Dog No. 14355 (Continued)

GROSS MICROSCOPIC Liver: No alterations observed. Hepatocytes in centrilobular and midzonal portions of lobules much lighter in staining intensity than those at the periphery. A few areas of fibrosis and chronic inflammation in subcapsular locations. Kidney: No alterations observed. One tiny area of chronic interstitial nephritis. No tubular dilatation. Bone Marrow: No alterations observed. Low numbers of megakaryocytes. Erythroid and myeloid maturation complete. Small amounts of pigment.

Activity moderate.

#### GROUP NO. 2 Female Dog No. 14457

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Medium- and large-sized follicles predominated.

Colloid bright eosinophilic.

Follicles lined by flattened to low cuboidal

epithelium.

Functional activity judged to be low.

Gallbaldder:

Could not be located grossly.

Section not available for microscopic examination.

Spleen:

No alterations observed.

Follicles appeared normal.

Much greater abundance of reticuloendothelial

tissue than lymphoid tissue.

Megakaryocytes infrequently seen.

Occurrence of pigment within red pulp very low.

Liver:

No alterations observed.

Mild chronic pericholangitis.

Very slight amount of periportal fibrosis.

Kidney:

No alterations observed.

Minimal areas of chronic interstitial nephritis

and tubular dilatation in cortex.

In one of the affected areas, dilated tubules

lined by flattened or low cuboidal epithelium

and devoid of any material in their lumens.

Slight chronic pyelitis.

## GROUP NO. 2 Female Dog No. 14457 (Continued)

Urinary Bladder:

Neck of bladder red.

Not remarkable.

Bone Marrow:

No alterations observed.

Erythroid and myeloid maturation complete.

Small numbers of megakaryocytes.

Very little pigment present.

Activity of the marrow appeared to be low.

## GROUP NO. 3 Female Dog No. 14417

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Moderate- or large-sized follicles predominated.

Colloid predominantly brightly eosinophilic.

Follicles lined by flattened or low cuboidal

epithelium.

Functional activity of thyroid based on

histologic criteria was low.

Spleen:

No alterations observed.

Lymphoid follicles appeared normal.

The bulk of the splenic tissue composed of

reticuloendothelial tissues.

Megakaryocytes occasionally seen.

Minimal of pigment within red pulp.

Kidney:

No alterations observed.

Very minimal chronic interstitial nephritis.

Areas of tubular regeneration or tubular

dilatation not seen.

Bone Marrow:

No alterations observed.

Erythroid and myeloid maturation appeared

complete.

Erythroid hyperplasia present.

Red blood cell precursors very numerous.

# GROUP NO. 3 Female Dog No. 14417 (Continued)

GROSS

MICROSCOPIC

Numbers of megakaryocytes very numerous.

Small amount of pigment.

The following organs were not altered grossly or microscopically: liver and urinary bladder.

#### GROUP NO. 3 Female Dog No. 14435

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Large- or medium-sized follicles predominated.

Colloid brightly eosinophilic.

Thyroid follicles lined by low or flattened

cuboidal epithelium.

Activity of thyroid low as judged by histologic

criteria.

Gallbladder:

Distended.

Scattering of lymphocytes and plasma cells

in the submucosa, but no well-defined

follicles.

Spleen:

No alterations observed.

Lymphoid follicles normal.

Reticuloendothelial tissue much more abundant

than white pulp.

Occasional megakaryocytes.

Slight amounts of pigment within red pulp.

Kidney:

No alterations observed.

Moderate tubular regeneration and tubular

dilatation, primarily, involving the cortex.

Occasional foci of chornic interstitial nephritis.

Occasional glomeruli appeared sclerotic.

### GROUP NO. 3 Female Dog No. 14435 (Continued)

**GROSS** 

MICROSCOPIC

Transitional epithelium lining the renal pelvis, vacuolated in focal areas, with infiltrations of neutrophils, and chronic inflammatory cells.

Within the submucosa diffuse collections of acute and chronic inflammatory cells and some lymph follicle formations.

Changes correspond to a subacute pyelitis.

Urinary Bladder:

No alterations observed.

Moderate chronic cystitis.

Mucosal epithelium was vacuolated with focal infiltrations by polymorphonuclear leukocytes.

Within the submucosa were many foci of chronic

inflammatory cells.

Many vessels in submucosa were congested.

Bone Marrow:

No alterations observed.

Erythroid and myeloid maturation appeared complete.

Only a few megakaryocytes seen.

Small amounts of pigment present.

Activity of the marrow appeared to be very low.

The following organs were not altered grossly or microscopically: liver and pancreas.

#### GROUP NO. 4 Female Dog No. 14458

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Moderate-sized follicles predominated.

Follicles lined by flattened or low cuboidal

epithelium.

Activity low.

Gallbladder:

Distended approximately

four times normal size.

Chronic cholecystitis with generalized

infiltration of the tunic propria with

lymphocytes and plasma cells.

Infiltration extended into superficial

muscular tunics.

Spleen:

No alterations observed.

Lymphoid forlicles normal in appearance.

Reticuloendothelial tissue predominated.

Amount of pigment in red pulp very low.

Megakaryocytes seen infrequently.

Kidney:

Capsular surface appeared

rough with some gray

discoloration.

Medulla reddened.

Slight chronic interstitial nephritis

invovling the cortex with the presence of

lymphocytes and plasma cells.

## GROUP NO. 4 Female Dog No. 14458 (Continued)

**GROSS** 

MICROSCOPIC

In affected areas, moderate numbers of cortical tubules dilated, but essentially devoid of proteinaceous sediment.

Moderate numbers of tubules in affected areas showed regenerative activity.

Fibrosis appeared minimal.

Intracytoplasmic, brown pigment found in very low quantities within cytoplasm of cortical tubules.

Minimal cast formation in medullary tubules.

Liver:

No alterations observed.

Focal chronic hepatitis in sections of liver adjacent to gallbladder section.

Mild periportal chronic inflammation.

Eye:

No alterations observed.

Severe conjunctivitis with focal ulceration of

conjunctival epithelium.

Large lymphoid follicle formations in the subepithelial tissues of the palpebral conjunctiva near the limbus inflammatory cell adhered to the cornea.

Other structures not remarkable.

Pancreas:

No alterations observed.

Vacuolar pancreatopathy similar to that described in male Dog No. 14494.

# GROUP NO. 4 Female Dog No. 14458 (Continued)

GROSS MICROSCOPIC

Urinary Bladder:

No alterations observed.

Slight congestion of the submucosal vessels;

otherwise, not remarkable.

Ovary:

No alterations observed.

Many oocytes within small follicles in the cortex.

Corpora lutea not seen.

Uterus:

No alterations observed.

Small section included for examination not

remarkable.

The following organs were not altered grossly or microscopically: brain, spinal cord, pituitary, adrenal, heart, lung, stomach, large intestine, mesenteric lymph node, nerve with muscle, and rib (bone).

### GROUP NO. 4 Female Dog No. 14468

GROSS

MICROSCOPIC

Thyroid:

No alterations observed.

Small- and medium-sized follicles predominated.

Colloid within follicles brightly eosinophilic.

Follicles lined by flattened or low cuboidal

epithelium.

Activity moderate.

Gallbladder:

No alterations observed.

No section available for examination.

Spleen:

No alterations observed.

Lymphoid follicles appeared normal.

Reticuloendothelial tissues comprised the

bulk of the organ.

Very few megakaryocytes.

Small amount of pigment in red pulp.

Liver:

No alterations observed.

Minimal vacuolation of hepatocytes in periportal

locations.

Kidney:

No alterations observed.

Moderate areas of interstitial nephritis chiefly

in cortex.

In these areas, small numbers of dilated tubules

which occasionally contained a small amount

of eosinophilic granular sediment.

### GROUP NO. 4 Female Dog No. 14468 (Continued)

GROSS

#### MICROSCOPIC

Moderate numbers of tubules undergoing regeneration, small with closely crowded nuclei.

Small amounts of lymphocytes and plasma cells infiltrated affected areas.

Small amount of brown, granular pigment in some tubules in affected areas.

Small numbers of glomeruli in which basement membrane of glomerular tuft thickened.

Other glomeruli atrophic.

Urinary Bladder:

No alterations observed.

Slight congestion of submucosal vessels; otherwise, not remarkable.

Uterus:

No alterations observed.

Minimal focal endometritis with small numbers of

polymorphs within uterine glands.

Affected glands surrounded by small numbers of reticuloendothelial and lymphocytic cells.

Ovary:

No alterations observed.

Many oocytes within small follicles occupying

the cortex.

Corpora lutes not seen.

# GROUP NO. 4 Female Dog No. 14468 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Erythroid and myeloid maturation of cells

Megakaryocytes numerous.

Pigment moderate in amount.

Hematogenic activity moderately high.

The following organs were not altered grossly or microscopically: brain spinal cord, pituitary, liver, adrenal, eye, heart, lung, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, nerve with muscle, and rib (bone).

complete.

GROUP NO. 5 Female Dog No. 14470

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Majority of follicles large or medium size.

Colloic brightly eosinophilic.

Follicles lined by flattened or low cuboidal

epithelium.

Thyroid activity according to histologic

criteria appeared to be low.

Eye:

No alterations observed.

Globe partially collapsed.

Cornea wrinkled.

Lens badly shattered.

Parts of retina and choroid disrupted or

detached.

Lung:

No alterations observed.

Artifactual compression of alveolar septa.

Spleen:

Enlarged.

Autolysis; impossible to evaulate.

Liver:

Pale appearance.

Diffuse, fine vacuolation of hepatocytes.

Congestion.

Autolysis.

## GROUP NO. 5 Female Dog No. 14470 (Continued)

**GROSS** 

MICROSCOPIC

Kidney:

No alterations observed.

Large numbers of dilated tubules within cortex and outer medulla.

Dilated tubules for the most part empty, but occasionally a small amount of pink, granular, exudate within lumens.

Dilated tubules lined by flattened or low cuboidal epithelium.

Occasional minute foci of chronic interstitial nephritis.

In inner medulla, the presence of pink, proteinaceous cast within tubules was more apparent.

Mesenteric Lymph Node:

No alterations observed.

Section missing.

Bone Marrow:

No alterations observed.

Normal erythroid and myeloid cell maturation.

Megakaryocytes moderately numerous.

Presence of pigment very low.

Overall activity of marrow judged to be low.

The following organs were not altered grossly or microscopically: brain, pituitary, adrenal, heart, gallbladder, stomach, small intestine, large intestine, pancreas, urinary bladder, overy, nerve with muscle, and bone.

#### GROUP NO. 5 Female Dog No. 14471

**GROSS** 

MICROSCOPIC

Thyroid:

No alterations observed.

Thyroid follicles predominantly large or

medium size.

Colloid brightly eosinophilic.

Follicles lined, for the most part, by

flattened or low cuboidal epithelium.

Overall activity judged to be low.

Adrenal:

No alterations observed.

In focal areas, cells of the zona glomerulosa

very vacuolated.

In a few cases, it appeared that continuous

cell borders had ruptured, leaving small

cystic areas.

Eye:

No alterations observed.

Artifacts present.

Globe partially collapsed.

Cornea wrinkled.

Lens badly shattered.

Segments of retina detached.

Significant histopathologic changes not observed.

### GROUP NO. 5 Female Dog No. 14471 (Continued)

GROSS

MICROSCOPIC

Spleen:

Enlarged.

Lymphoid follicles few in number.

Moderate numbers of polymorphs distributed

throughout red pulp.

Amount of pigment within red pulp very low.

Liver:

No alterations observed.

Generalized congestion; otherwise, not remarkable.

Kidney:

No alterations observed.

Moderately great numbers of dilated tubules predominantly in cortex but to a lesser extent within medulla.

These tubules, for the most part, are empty but occasionally contained small amounts of pink, granular material within lumen.

Very minimal areas of chronic interstitial nephritis seen.

Dilated tubules lined by an intact, flattened or low cuboidal epithelium.

Granular and hyaline casts more numerous in tubules in the inner medulla.

## GROUP NO. 5 Female Dog No. 14471 (Continued)

GROSS

MICROSCOPIC

Bone Marrow:

No alterations observed.

Myeloid and erythroid maturation complete.

Megakaryocytes moderately numerous.

Only small amounts of pigment.

Activity moderate.

The following organs were not altered grossly or microscopically: brain, pituitary, heart, lung, gallbladder, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, uterus, ovary, nerve with muscle, and bone.

TRWO LIFE SCIENCES CENTER

#### SUMMARY

Twenty clinically healthy beagle dogs (10 males and 10 females) were divided randomly into five groups and administered the compound (WR 2823) intravenously once daily for 14 days at levels of 20 mg/kg (Group No. 2), 40 mg/kg (Group No. 3), 80 mg/kg (Group No. 4), and 160 mg/kg (Group No. 5). Dogs in Group No. 1 served as untreated controls and received only saline injections. After 14 days, the dogs in Groups No. 1, No. 2, No. 3, and No. 4 were necropsied. All of the Group No. 5 animals died following three or four doses of the compound. Designated tissues were collected and placed in 10% buffered formalin, except for testes which were placed in Bouin's fluid, and eyes which were usually placed in alcoholic formalin. The eyes from Group No. 5 dogs were preserved in 10% neutral formalin. The following tissues were examined microscopically from two males and two females in each of Groups No. 1, No. 4, and No. 5: brain, pituitary, eye, thyroid, lung, heart, spleen, liver, gallbladder, kidney, adrenal, stomach, pancreas, small intestine, large intestine, urinary bladder, mesenteric lymph node, testis, ovary, prostate, uterus, rib (bone), and bone marrow. Sections of thoracic spinal cord from Groups No. 1 and No. 4 were also examined microscopically. From the dogs in Groups No. 2 and No. 3, the thyroid, liver, spleen, kidney, bone marrow, and unusual lesions were examined microscopically. Except for the Group No. 5 animals, all the dogs were catheterized, and a urine sample collected on the day before euthanasia.

AD-ALIS 856 HAZELTON LABS AMERICA INC. VIENNA VA TOXICITY STUDIES ON ANTIRADIATION AGENTS, (U) MAR 79 F E RENO F/G 6/20. DADA17-69-C-9105 UNCLASSIFIED NL 5 > 7

A definite, compound-associated nephropathy was seen in Groups No. 3 and No. 4 animals. The typical triad of changes consisted of chronic interstitial nephritis, tubular regeneration, and tubular dilatation and were seen in all Group No. 4 dogs and from two dogs in Group No. 3. In some cases, the regenerating tubules contained an increased amount of brown, intracytoplasmic pigment. In three of the Group No. 2 animals, one or more of these same histopathologic changes were seen, but the lesions were very minimal. There is a good likelihood that the renal lesions in Group No. 2 dogs were compound related, especially since they resembled the triad of histopathologic changes which occurred in Groups No. 3 and No. 4 dogs, and also because there was an absence of histopathologic changes in the kidneys of the control dogs. Histopathologic interpretation was difficult in the Group No. 5 animals, since they died after receiving two or three injections of the compound; and the tissues, in some cases, showed autolytic changes. In three of the five kidney sections from the Group No. 5 animals, there were pronounced tubular dilatation and the presence of renal tubular cast formation. Given sufficient time, these renal lesions may have progressed to the spectrum of histopathologic changes seen in Groups No. 3 and No. 4 dogs. There were neither significant inflammatory changes nor unequivocal nephrotic lesions in the kidneys of Group No. 5 dogs. The occurrence of acute cystitis and hemorrhage in urinary bladders from dogs in Groups No. 1 (two dogs), No. 2 (two dogs), and No. 4 (two dogs) was probably due to the catheterization procedure on the day preceding on the termination of the experiment. Two Group No. 3 dogs and one Group No. 4 dog had subscute or chronic cystitis which also appeared to be unrelated to the compound administration.

The compound-related conjunctivitis seen grossly was confirmed microscopically. Incidental findings in Group No. 4 dogs (not compound related) consisted of endometritis (one dog), prostatitis (two dogs), and testicular degeneration (one dog). Pancreatic acinar changes in two Group No. 4 animals were unusual and difficult to characterize histopathologically. These changes consisted of a slight interstitial thickening or prominence with discrete cytoplasmic vacuolation. The vacuolated cells frequently occurred as discrete small nests or thin bands of cells in the interlobular areas of the acinar pancreas. The cell-type showing this vacuolation could not be identified with certainty. The significance of this histologic change was difficult to assess, since similar pancreatic alterations were seen infrequently in control dogs.

Incidental findings in tissues from control dogs consisted of cystic glands in the small intestine, hepatic cell vacuolation, and focal pancreatitis.

Rare or incidental histopathologic findings in the treated animals which were not believed to be compound induced included pituitary cyst, pulmonary congestion, chronic coleocystitis, pericholangitis, hepatic congestion, hepatocytic vacuolation, slight hepatic fibrosis, and chronic inflammation.

The microscopic appearances of the spleen, bone marrow, ovary, testis, pituitary, thyroid, adrenal, and mesenteric lymph node were comparable between control and treated groups. Sections of eye, heart, lung, gallbladder, small intestine, large intestine, nerve with muscle, rib bone, and stomach were not remarkable in the control or treated groups.

In the summary section of the Project No. 193-406 study, a compound-related enlargement of the spleen was reported in the Group No. 5 dogs. However, the presence of autolytic changes in the spleen prevented a detailed microscopic appraisal. Congestion of the spleen was observed microscopically in the Group No. 5 dogs, but this most probably does not represent a compound effect since these animals died and, further, were not exsanguinated as were the other dogs in the study.

### KEY TO DETAILED HISTOPATHOLOGY INCIDENCE TABLE

N = No Section

X = Not Remarkable

A = Autolysis

P or √ = Present or Taken

0 = Absent

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderate to Severe

5 = Severe

### DETAILED HISTOPATHOLOGY INCIDENCE TABLE

	MALES GROUP NUMBER											
		1		2		3	,	4		5		
ORGANS	14121	14125	14251	14253	14366	14389	14494	14502	14504	14515		
BRAIN	х	х			•		x	x	A	x		
PITUITARY Cysts	x		x				x	X	A	x		
THYROID  Level of Activity Epithelial Heighth Follicular Size	3 2 4	3 2 4	2 2 4	2 2 4	2 2 4	2 2 4	2 2 3	2 2 4	2 2-3 4	2 2 4		
ADRENAL Normal Activity	P	P					P	P	A P	P		
EYE Conjunctivitis Artifact	х	X					2	x	A 2	X		
HEART Epicarditis & Myocarditis	x	С					P	x	x	x		
LUNG Congestion	x	X						x	A P	x		
GALLBLADDER Cholecystitis	x	X				X	x	x	A	A		
SPLEEN Congestion	х	X	x	x	X	x	x	x	A P	A P		
LIVER Hepatitis Pericholangitis Fibrosis of Chronic Inflammation Vacuolation	x	x	X	P	X	x		P	A	P		
Congestion STOMACH	x	x		-			P	x	A	n		

### DETAILED HISTOPATHOLOGY INCIDENCE TABLE

	<u> </u>	MALES GROUP NUMBER											
		1 1			2		3		1 4		5		1
ORGANS	NUMBER	14121	14125	14251	14253	77671	14300	14389	14494	14502	14504	14515	
PANCREAS Vacuolated Interstitial Pancreatopathy Pancreatitis		ĸ	x						P	x	X	x	
SMALL INTESTINE Cystic glands		X	X							x	A	A	
LARGE INTESTINE		X	x							x	A	x	
MESENTERIC LYMPH NODE		X	x							X	A	x	
PROSTATE Prostatitis	:	X	X						P	P	A	N	
UTERUS Artilis of Endometritis													
TESTIS Testicular Degeneration	:	X	X						2	x	x	X	
OVARY Artifact													
NERVE WITH MUSCLE	:	K	N							x	x	x	
RIB	:	K	X							x	x	x	
BONE MARROW  Hematogenic Activity  Numbers of Megakaryocytes  Erythroid Hyperplasia	1	N	2 2	2 2	1	2	2 L	2 3	3 2	2 2	A	3 2	

### DETAILED HISTOPATHOLOGY INCIDENCE TABLE

		MALES										
	ĺ						GROU	JP NUM	BER			
	[	1					3		1 4		5	
ORGANS	ANIMAL	14121	14125	14251	14253	14366	14389	14494	14502	14504	14515	
URINARY BLADDER			x		x	x				A	x	
Acute Cystitis	ł	P		P				P				
Subacute or Chronic Cystitis	1						P		P			
Ulcerations		P										
Hemorrhage	- 1	P		P			P	P	P			
KIDNEY	- [	x	x		X					A		
Interstitial Nephritis	- 1			1		1	3	2	3	••	1	
Tubular Regeneration	- 1			ī		-	3 3	4	3		•	
Tubular Dilatation	1			1			3	4	3		5	
Cast Formation				_			•	•	,		P	
Pigment	Í							P	P		•	
Pyelitis	- 1							•	•	1		

# DETAILED HISTOPATHOLOGY INCIDENCE TABLE

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	<u> </u>	1	1 3	2	1 3	3		4	L	<u>.                                    </u>	
VI JA	14333	14348	14355	14457	14417	14435	14458	14468	14470	14471	
BRAIN	x	x					x	x	x	x	
PITUITARY Cysts	х	x	P				x	X	x	X	
THYROID Level of Activity Epithelial Heighth Follicular Size	2 2 3	2 2 4	2 2 4	2 2 4	2 2 4	2 2 4	2 2 3	3 2-3 2-3	2 2 4	2 2 4	
ADRENAL Normal Activity	P	P					P	P	P	P	
EYE Conjunctivitis Artifact	х	A					5	X	P	P	
HEART Epicarditis & Myocarditis	x	x					x	X	X	x	
LUNG Congestion	x						x	X	X	x	
GALLBLADDER Cholecystitis	x	X		N		x	P	N	x	x	
SPLEEN Congestion	A	X	X	x	x	x	x	x	A P	X P	
LIVER Hepatitis Pericholangitis			•	2 2	x	x	P			X	
Fibrosis of Chronic Inflammation Vacuolation Congestion	P	P	2	2			P		P		
STOMACH	x	x					x	x	x	X	

## DETAILED HISTOPATHOLOGY INCIDENCE TABLE

	i					F	EMALE GROU	S P NUM	BER.			
			1		2	11	3		4	<u> </u>	5	
organs_	ANTWAL NUMBER	14333	14348	14355	14457	14417	14435	14458	14468	14470	14471	
PANCREAS Vacuolated Interstitial Pancreatopathy Pancreatitis		1	x			1		P	x	X	X	_
SMALL INTESTINE Cystic glands		P	X						X	X	x	
LARGE INTESTINE		x	x					X	x	x	x	
MESENTERIC LYMPH NODE		X	x					X	x	N	X	
PROSTATE Prostatitis												
UTERUS Artifact Endometritis		X	P					X	1		x	
TESTIS Testicular Degeneration												
OVARY Artifact		X	P					X	x	X	X	
NERVE WITH MUSCLE		X	x					X	X	X	X	
RIB		X	x					x	x	x	X	
BONE MARROW Hematogenic Activity Numbers of Megakaryocytes Erythroid Hyperplasia		4	3	3 2	2 2	4	2 3	4 2	3	2	3	

## DETAILED HISTOPATHOLOGY INCIDENCE TABLE

	1				<del></del> -		FEMA	ES JP NUM	(RFR	<del></del>		
			<u> </u>		2	1 3	L	1 4			5	I
ORGANS	ANTMAL NUMBER	14333	14348	14355	14457	14417	14435	14458	14468	14470	14471	
									-			
URINARY BLADDER			X		X	X		X	X	X	X	
Acute Cystitis		P					P					
Subacute or Chronic Cystitis Ulcerations							r					
Hemorrhage		P										
Hetho! Illege		-										
KIDNEY		x	X									
Interstitial Nephritis				1	1	1	2	2	3	1	1	
Tubular Regeneration				1			2 3	2 3	3 3 2			
Tubular Dilatation					1		3	3	2	5	4	
Cast Formation								P		P	P	
Pigment	- [					P	_	P	P			
Pyelitis	1						5					

#### HAZLETON LABORATORIES, INC.

TRW LIFE SCIENCES CENTER

Sponsor: Walter Reed Army Institute of Research

Date: September 30, 1970

Material:

WR 2823 AC (AU 69115)

Lot No: WR 8-55D

BV-WR-01

Subject:

REPORT NO. 38

WR 2823 AB

Two-Week Intravenous Toxicity Study - Rats

Project No. 193-412

#### SUMMARY OF FINDINGS

This study was conducted to evaluate and compare the effects of shoterm intravenous administration of WR 2823 AC (AU 69115) and WR 2823 AB in m. and female albino rats.

Criteria evaluated for compound effect were physical appearance and behavior, body weight gains, food consumption, survival, clinical laboratory results, and gross and microscopic findings at necropsy.

The following signs were observed in the test rats after the daily dose: depression, watery eyes, sleepy appearance, and a heart beat of normal rate but increased depth or intensity. Group No. 3 (WR 2823 AB) rats also exhibited cold extremities.

Growth and food consumption were depressed in test males, but were generally comparable between test and control females.

Except for higher blood sugar values obtained for the male and female test groups at one and two weeks, the results of the clinical laboratory values for the test groups were generally comparable with those for the control rats.

At necropsy the following observations were made: dark red areas on the lobes of the lungs (nine controls, four Group No. 2 rats, and eight Group No. 3 rats); small abscessed and/or consolidated areas on the lobes of the lungs (three controls, two Group No. 2 rats, and two Group No. 3 rats); dark pink lungs (one Group No. 2 rat); gray, cyst-like areas on the lungs (one Group No. 3 rat); dark pink, red, or brown outer renal medullas (four controls, nine Group No. 2 rats, and 11 Group No. 3 rats); dilated renal pelves (two controls and two Group No. 2 rats); dark red zone between renal cortices and medullas (two Group No. 2 rats); pale, gray-brown, green-brown, or yellow-brown renal cortices (four Group No. 2 rats and two Group No. 3 rats); thick, yellow substance in the renal pelves (one Group No. 2 rat); yellow foci in the duodenal lining (one Group No. 3 rat); and distended uterine horns filled with clear fluid (two controls and one Group No. 3 rat).

Statistical analysis of terminal body weights, organ weights, and organ/body weight ratios revealed significantly lower terminal body weights for test males than for controls, significantly lower heart weights for test males than for controls, significantly lower testes weights for Group No. 2 males than for controls, and a significantly higher adrenal/body weight ratio for Group No. 2 males than for controls.

Histopathological examination of selected tissues failed to show any distinct, compound-related alterations; and no significant differences were observed in rats treated with the two samples of WR 2823.

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#### **MATERIALS**

## Identification

WR 2823 AC (AU 69115): Lot No. WR 8-55D.

WR 2823 AB: Lot No. BV-WR-01.

## Description

WR 2823 AC (AU 69115): A fine, white powder; no odor noted.

WR 2823 AB: White, solid material in sterile, sealed vials.

Receipt Both from Walter Reed Army Institute of Research on June 11, 1970.

Purity Considered 100% active ingredient.

#### **METHODS**

Experimental Animals Seventy-two healthy albino rats, 36 males and 36 females,

of Charles River Caesarean-derived strain.

Weight Range at Initiation: For the males from 180 to 205 grams and for the females from 162 to 190 grams.

Housing: Individually in elevated wire mesh cages.

Diet: Purina Laboratory Chow and water available ad libitum.

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## Animal Groups and Dosage Levels

Method of Grouping: Stratified randomization.

Group No.	No. of	Animals female	Treatment	Dosage Level mg/kg/day
1 (Vehicle Control)	12	12	Saline	-
2	12	12	WR 2823 AC	60
3	12	12	WR 2823 AB	60

## Preparation of Solutions

Vehicle: 0.9% sterile saline.

Concentration: 60 mg. of the test compound per milliliter of vehicle for Groups No. 2 and No. 3. The solution of saline and compound WR 2823 AC which was administered to Group No. 2 animals was kept refrigerated and allowed to warm to room temperature before dosing. The solution of saline and WR 2823 AB which was administered to Group No. 3 animals was prepared fresh daily, and the test powder was kept in the freezer.

## Drug Administration

Each test rat received a daily intravenous injection via the lateral tail vein of 60 mg. of test compound per kilogram of body weight at a volume of 0.1 ml. per 100 grams of body weight. Dosages were adjusted daily on the basis of individual body weights. Control animals were dosed with a volume of saline equivalent to that received by the treated groups.

All rats received 15 consecutive daily injections. Seven males and seven females from the control and high level groups were sacrificed on the second day following the last dose. The other 44 animals were sacrificed on the day following the last dosage; no dosages were administered on the day of sacrifice.

#### Observations and Records

Daily: For signs of toxic or pharmacologic effect with special attention to heart rate, body temperature, and coloration.

Weekly: Food consumption. Individual body weights were taken daily for the purpose of dosage adjustment but are recorded weekly in this report.

#### Clinical Laboratory Studies

Intervals: Initially, at one week, and at two weeks (terminal).

Methods: Performed on five rats of each sex from each group; blood samples were obtained from the tail vein (from the abdominal aorta for biochemical studies at sacrifice). Urine samples were collected from rats housed overnight in individual metabolism cages and pooled by groups.

Hematology: Erythrocyte count, total and differential leukocyte counts, hematocrit, hemoglobin, and prothrombin and coagulation time determinations.

Biochemistry: Fasting blood sugar, blood urea nitrogen, serum glutamic-pyruvic transaminase, and alkaline phosphatase determinations.

Urine Analysis: Appearance, pH, specific gravity, sugar, protein, bilirubin, occult blood, and microscopic examination of the sediment.

Ophthalmologic Examinations Conducted on all rats assigned to the study initially and at termination, prior to sacrifice, using "Mydriacyl" (Alcon) and a binocular, indirect ophthalmoscope.

### Terminal Studies

Terminal Sacrifice: Performed on each rat one day (five males and five females from controls and Group No. 3 and all Group No. 2 rats) or two days (seven males and seven females from controls and Group No. 3) after the last injection (the 15th dose).

Method - Exsanguination under Diabutal anesthesia.

Gross Observations - Recorded at necropsy for each rat.

Organ Weights (Determined For Each Rat) - Thyroids, liver, kidneys, spleen, heart, adrenal, testes with epididymis, and ovaries. (Thyroids and adrenals weighed after fixation.)

#### Tissues Preserved From Each Rat:

In 10% Neutral Buffered Formalin - Brain, pituitary, spinal cord, thyroid, lung, heart, liver, spleen, kidney, ureter, urinary bladder, adrenal, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, testis, prostate, ovary, uterus, bone marrow, bone, and injection site.

In Alcoholic Formalin - Eyes.

Histopathological Examination: From five males and five females in each group, all tissues listed above under "Tissues Preserved From Each Rat," with special attention to the kidney, ureter, bladder, and cornea.

All tissues are being held at Hazleton Laboratories, Inc., for possible future reference.

## Statistical Evaluation

Criteria: Terminal body weights, organ weights, and organ/body weight ratios.

Method: Analysis of variance, or F-test, at the 5.0% probability level;

preliminary tests (where applicable) by methods of Bartlett, Scheffe,

and Fisher-Behrens (modified t-test).

#### RESULTS

## Gross Appearance and Behavior

Transient signs included urine stains in one Group No. 2 male and female and one Group No. 3 male, wheezing in one control male and female and in two males and two females from Group No. 2, nasal discharge in one control female and one Group No. 3 male, soft feces in one control male, and bloody crust on the eyes or nose of two Group No. 3 males.

One male and six females from Group No. 2 and one male and two females from Group No. 3 exhibited alopecia after approximately one week of dosing. One Group No. 1 female, one male and six females from Group No. 2, and two Group No. 3 females exhibited hunched posture, generally toward the end of the study.

A few minutes after they were dosed, Groups No. 2 and No. 3 rats showed depression, watery eyes, and sleepy behavior. The heartbeat of these rats continued at a normal rate after dosing, but the beat was noticeably deeper or stronger. In addition, Group No. 3 rats exhibited cold extremities shortly after dosing.

## Growth, Food Consumption, and Survival

Mean weekly body weight and food consumption data are presented in Table No. 1.

Weight gains and food consumption for Groups No. 2 and No. 3 males were lower than those for control males. Body weight gain and food consumption were comparable among female control and test groups. Survival was 100%.

#### Results of Ophthalmoscopic Examination

Gross ophthalmoscopic examinations were performed on all rats at initiation and prior to sacrifice. At initiation, no gross abnormalities were observed in any rat. At termination a small, corneal opacity adjacent to the nasal canthus was observed in the right eye of female Rat No. 86-586 from Group No. 1 (control) and the left eye of female Rat No. 86-613 from Group No. 2. The eyes of the remaining 70 rats appeared grossly normal at termination.

#### Clinical Laboratory Studies

The results of these studies are presented in Tables No. 2 (hematology), No. 3 (biochemical values), and No. 4 (urine analyses).

The hematological values determined at one and two weeks for the male and female test groups showed no significant differences from control values, and no dose-related trends were apparent. Except for a few slightly decreased or elevated individual values obtained for control and test rats, all values were comparable among the test and control groups.

A trend toward higher blood sugar values was evident at Week 1 and Week 2 in the male and female test groups when compared with control rats. The two-week blood sugar values showed an overall increase in all groups including controls when compared with the blood sugar values at Week 1.

Other biochemical values and the results of urine analysis were comparable among the test and the respective control groups.

#### Gross Observations at Necropsy

The following gross alterations were observed at necropsy: dark red areas on the lobes of the lungs were observed in four control males and five control females, two males and two females from Group No. 2, and four males and four females from Group No. 3. Small, abscessed and/or consolidated areas on the lobes of the lungs were noted in one control male and two control females, two Group No. 2 males, and one male and one female from Group No. 3. The lungs of one Group No. 2 female were dark pink; and the lungs of one Group No. 3 male contained gray, cyst-like areas. None of the above findings are considered compound related.

Dark pink, red, or brown outer renal medullas were noted in three control males and one control female, four males and five females from Group No. 2, and six males and five females from Group No. 3. Dilated renal pelves were observed in one male and one female each from Groups No. 1 and No. 2. A dark red zone was observed between the renal cortices and medullas of one male and one female from Group No. 2. Pale, gray-brown, green-brown, or yellow-brown renal cortices were noted in two males and two females from Group No. 2 and one male and one female from Group No. 3. The renal pelves of one Group No. 2 female contained a thick, yellow-green substance.

Yellow foci were observed in the duodenal lining of one Group No. 3 male. The horns of the uterus were distended with clear fluid in two control females and one Group No. 3 female.

## Organ Weights

Mean terminal body weights, organ weights, organ/body weight ratios, and their standard deviations for all males and females are presented in Table No. 5.

Statistical analysis revealed the following values for the rats in the test groups to be significantly different from values for the control animals.

Summary of Table No. 5
Significantly Different Values For Test Groups
As Compared to Control Group

	Mai	les
Organ	Group No. 2 Receiving WR 2823 AC	Group No. 3 Receiving WR 2823 AB
Terminal body weight	s-	S-
Heart weight	S-	S-
Testes weight	s-	
Adrenal/body weight ratio	<b>\$+</b>	

S- = Significantly lower than control

S+ = Significantly higher than control

#### Histopathological Examination of Tissues

Unequivocal, compound-induced changes were not seen in the study.

Histopathologic findings among control and treated groups which did not vary significantly in their incidence or severity were chronic murine pneumonia, nonsuppurative epididymitis, nonsuppurative hepatitis and pericholangitis, and focal pancreatitis. Rare lesions in control or treated groups consisted of mild chronic interstitial nephritis, Harderian gland adenitis, and prostatitis. The occurrence of epicarditis and focal myocarditis were considered spontaneous lesions unrelated to the compound administration. The occurrence of glial nodules, nonsuppurative meningitis, and perivascular lymphocytic cuffs in the brain resemble those lesions described in murine nosematosis, a latent, clinical occult infection in this species.

An extracellular vacuolation in spinal cord and brain was seen in some control and treated animals. The vacuoles either appeared empty or contained gray, birefringent, granular material. These changes probably represent histologic artifacts.

Sections of spleen, ureter, urinary bladder, stomach, small intestine, large intestine, mesenteric lymph node, and bone were generally not remarkable. Sections of bone marrow, thyroid, and adrenal appeared comparable microscopically in control and treated groups. Other cytologic changes described in the detailed pathology, protocol, or listed on the incidence tables are considered incidental findings and not related to administration of the compound. Examination of the injection site revealed no marked or consistent differences between the treated and control animals.

In summation, the administration of compounds WR 2823 AC and WR 2823 AB to male and female rats for two weeks by intravenous injection did not produce unequivocal, compound-induced changes in the tissues examined.

The incidence tables are presented as an addendum. The detailed histologic findings are on file at Hazleton Laboratories, Inc.

Submitted by

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Director, Drugs and

Industrial Chemicals Department Toxicology-Biosciences Laboratory

Pathology by

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Staff Pathologist

Report Preparation: Spruill

Supervision: Elliott

gbb

## EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

- $T = trace (\pm)$
- 0 = negative
- 1 = slight (+)
- 2 = moderate (++)
- 3 = marked (+++)
- 4 = severe (++++)
- V T YEL = very turbid yellow

Table No. 1 – Mean body weights, weight ranges, food consumption, and survival data for ( 🕅 male, 📋 female) albino rats.

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Table No. 1 – Mean body weights, weight ranges, food consumption, and survival data for (  $\square$  male,  $\boxtimes$  female) albino rats.

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TARLE O. 2 - HENNYDHAL TREATOURIEL VALUES ALREGO RATS GR 2 RECEIVING "11 2523 AC & 68 3 RECEIVING DE 2823 AU FOR TOU "1155 FOLTAL

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TABLE PUS 2 - IPPIMIDAL HEARTHOOLGAL VALUES ALBLO RATS GR 2 RECEIVING PR 2823 AC 8 GR 3 RECEIVING MA 2823 AR FUR TOO PERIS URBA 1

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TABLE POLE OF 3 - TOTVIDOAL BUIDD COPOLSTRY VALUES
ALBEDO RATS GR 2 CECPTVIDG OR 2623 AC 5 GR 3 RECGIVING OR 2623 AC FOR POLICES
LATIAL

ALK PIAIS K-A DELTS	70.4	76.4	0.09	68.4	2.60	689	52.0	63.2	0.09	53.2	66.4	0.05	50.6	87.6	51.2	38.4	80.8	55.4
SGPT R-F.	41.0	38.0	33.0	39.0	38.0	38.8	41.0	29.0	36.0	38.0	35.0	36.8	41.1	38.0	35.0	41.0	38.0	38°0
800 800	17.0	16.0	17.0	16.0	12.0	15.6	15.0	14.0	14.0	13.0	15.0	15.0	13.0	16.0	18.0	16.0	13.0	15.2
6LUCUSE PGS	54.0	44.	42.0	52.0	41.0	4.6.6	75.0	86.0	88.0	80.0	82.6	87.2	30.0	e 5 • C	0.29	61.0	37.0	90.00
N H X	=	Ξ	=	Ξ	Ξ		Ξ	z	Ξ		Ξ		:	-		Ξ	.:	
APTPAL PURBER	86571	86572	86573	97.598	86575	IEAN	<b>8659</b> 5	96598	86597	86598	86599	PEAP	51998	8662)	86621	22503	82998	FAN
GAUMP PUBLER	•	<b>-</b> -i	_	1	7	GROUP HEAM	^	61	$\sim$	$\sim$	~	i daaa	æ	55.	n	m	çe,	HARTHY LEAN

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TASLE MU. 5 - LEDIVIDUAL SLAMO GARALSTRY VALUES AUTORIO RATS GRIZ REGEIVITO UR 2823 AUTORIO GRIZ RECEIVITO UR 2823 AR FUR TUR SERIES VEEK I

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ALK.PHUS K-A.UPTS	04), 6:	0 79	* * * * * * * * * * * * * * * * * * *	† * * * * * * * * * * * * * * * * * * *	0.05 20.05	6.84	7 17	) . 	7 • 1 • 1		7.8.5	3.5	68.3	х <b>У</b> 7		6.0.5		00 00 00 00 00	0°25
S62T R-F.	61.0	34-0	) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) (		47.0	39.8	0,00	44. ()	46.0			0.76	40. ×	41.6	0.00	(, 4,7,7	47.0	0.[7	40.4 X
18 Hit	16.0	17.0	14.0	15.0	15.0	15.6	16.0	10.0	17.0	16.0	10.01	0.07	16.2	13.0	0.64	16.0	0.8	14.0	16.0
et ucose	43.0	0.76	25.0	37.0	36.0	36.6	96.0	73.0	75.0	2000	7.1 0		79.4		77.0				
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APT PAL PUNB PR	36571	86572	86573	86574	91.598	EAN	86595	98598	86597	86598	86599		EAm	36619	(2908	8662]	36622	82996	EATO
GROUP FOURTHER	_	7	<b>,_</b>		-	бкилр БЕАП	~	~	2	~	2		eritte ream	m.	in.	M	гc.	w	CROW LEAD

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TABLE PU. 5 - TEPIVIDIAL BLIOD CREATSTRY VALUES ALELEO KAIS GR 2 RECEIVIDG OR 2823 AC 8 GR 3 RECEIVIDG OR 2923 AR FUR PERS RETTAL

ALK.PHUS K-A.UNITS	39.2	33.2	8.03	26.0	24.4	32.7	61.2	0.09	0.89	60.0	53.2	60.5	63.2	50.4	9.1.4	54.8	33 • C	49.9
SGPT R-F.	41.0	38.0	38.0	38.0	38.0	37.4	39.0	38.0	41.0	35.0	42.0	39.0	38.0	35.0	37.0	50.0	32.0	37.4
810a n633	20.0	22.0	0.12	16.0	17.0	19.2	0.6%	0.02	0.1%	0.02	20.0	22.0	37.0	22.0	27.0	32.0	0.82	28.82
GLUCOSE 1165	127.0	85.0	37.0	92.0	86.6	0.46	0.95	0.60	0.7.4	0.63	70.07	5.08	84.0	73.0	36.0	79.0	0.8°	5) • <del>1</del> 0
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APELOAL PIUJE ER	86563	86584	20508	86586	13698	LEAM	7 (M) H	5660 B	96619	45610	86611	e£Ar!	86631	86438	86993	50000	46997	PAN
GROUP MU 3 FR		~	-	1	<b>~</b>	GRUUP	$\sim$	^	~	N.	~	GRIMP	50	,c	ж.	ъ.	æ	GROUP CEAS

TAPLE CONTROL STATES AND TRANSPORTED TO STANDAR SERVICE AND SERVICES OF THE TERROL OFFICE AND THE SERVICES OF THE SERVICES OFFICE OFFIC

ALK PHUS K-A-HeltS	\$ \$ X	9. (2	74.4	20.07	22.4	53.4	21.6	5 · 3 · 3 · 3 · 3 · 3 · 3 · 3 · 3 · 3 ·	2		18.0	24.4	45.66	. N		\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	5 S	90.08
SGPT R-F.	62.0	(44.00)	36.0	39.0	46.0	45.4	38.0	34.0	0.7.4	53.0	46.0	6.61.45	62.0	40.04	42.0	46.0	41.0	66.0
1911-4 1913-1	0.92	71.0	18.0	15.0	17.0	19.4	0.82	0.02	17.0	27.0	18.0	22.0	24.0	20.02	17.0	18.0	20.05	19.3
GLUCUST ISBS	05.0	1) • 25	30.0	53.0	49.0	2.64	61.0	1,00	103.0	126.0	96.0	97.6	112.0		72.0	74.0		\$ · 85
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Astrock Milesen	86583	X6534	86535	86586	86567	EAL	86607	8 0998	36.009	86610	86611	Erit	86651	86632	56633	86634	86635	EVIII
GROUP THE BE	_	<b>.</b>	,	<del></del>	~	GKONP READ	^	Λ.	∕.	N	N.	GROUP TIEFT	N.		;c	m	añ.	СЕСИНР ИЕЛИ

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TASTE 100. 4 - ORTAF AGALYSIS ALSTEO RATS GR 2 RECEIVING OR 2823 AC & GR 3 RECEIVING OR 2823 AB FOR THO OBERS IMITIAL

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TABLE DO. 4 - DOLDE ANALYSIS ALBIAO KATS GR 2 RECEIVIPG OR 2823 AC & GR 3 RECEIVIEG OR 2823 AB FOR TOUREEES ALBIAO KATS GR 2 RECEIVIPG OR 2823 AB FOR TOUREES

BICROSCOPIC FIMDIACS BC - BBC - EPITH ADMIRPH CRYS BACT SPERO	TIMEY WITH	FEB DIADY	HALLY BEALEY
I CRUSCO EPITH	0-3	3-5	2-3
HEC.	3-4	4-5	2-3
145.6	2-3	2-0	1.
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SID PROFEILIT OCC GAR TEIN RUBIN BLD	0	О	С
PRO- TEIN	c	9	<u>;</u>
S11- 6AR	5	c	9
P SP.GR. GAR TEIG RUBIE BLD REG	7 1.008 0 0 0 0 2-3 3-4 0-3	6 1,004 0 0 0 0-2 4-5 3-5	7 1.009 0 T 0 0 1-3 2-3 2-3
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\* = PHILTO SALPLES

TABLE 20. 4 - UPINE ABALYSIS ALBIEN KAIS GR 2 RECEIVING PR 2823 AC & GR 3 RECEIVING UR 2823 AB FOR THO OFFES IDITIAL

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# # PUBLIC SAMPLES

TABLE PUT 4 \* \* URINE ABALYSIS ALBIPO KATS GR 2 RECEIVIPO BR 2823 AC 8 GR 3 RECEIVING BR 2823 AB FOR THO SPEKS DEEK 1

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SU- GAR	C	င	С
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APPEAR.	5% F T YEL	5* F T YFL	S* F T YEL
COLUMER S GAROD OF AST F AULSER (CALS X	ш # #	Œ ₩	ж. Ж
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\* = PHOLEO SACPLES

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TABLE NO. 5- MEAN TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, ORGAN/BODY WEIGHT RATIOS, AND STANDARD DEVIATIONS FOR MALE AND FEMALE ALBINO RATS.

ALBINO RATS GR 2 RECEIVING WR2823 AC & GR 3 RECEIVING WR2823 AB FOR TWO WEEKS

				43/			
	N 96	0.041	0.050	43/	0.04	90.0	0.04
RT	RAT 10	0.430	0.423	0.409	0.45	0.43	0.44
HEART	<b>တ</b> ဖိ	0.11	1.13 <sup>S-</sup> 0.16	1.16- 0.12	60.0	0.19	0.08
	WEIGHT 6.	1.30 0.11	1.138-	1.16 <sup>S-</sup>	96.0	0.89	0.92
	N 96	0.0015	0.0013	0.0008	0.0014	0.0019	0.0012
THYROID	RAT10	0.0076	0.0076	0.0070	9600.0	0.0094	0.0088
THY	v •	0.005	0.004	0.003	0.003	0.004	0.003
	₩Е I GHT 6•	0.023 0.005	0.020	0.020 0.003	0.020 0.003	0.020	0.019
	ۍ د د	14	15	15	10	15	13
BODY WEIGHT	WEIGHT G.	30 4	268 <sup>S-</sup>	285 <sup>S-</sup>	213	211	211
80	z	12	12	12	12	12	12
	SEX	Σ	I	£	u.	u.	<b>L</b>
	GROUP NUMBER		2	m	-	7	M

S- = SIGNIFICANTLY LOWER THAN CONTROL

TABLE NO. 5- MEAN TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, ORGAN/BODY WEIGHT RATIOS, AND STANDARD DEVIATIONS FOR MALE AND FEMALE ALBINO RATS.

ALBINO RATS GR 2 RECEIVING WR2823 AC & GR 3 RECEIVING WR2823 AB FOR TWO WEEKS

		4	432	-				
	<b>∞</b> 3€	90.0	432 *:	0.07	0.08	90.0	0.11	
SPLEEN	RATIO %	0.27	0.26	0.25	0.30	0.28	0.32	
SPL	v ç	0.18	0.18	0.22	0.18	0.12	0.22	
	WEIGHT G.	0.83	0.74	0.72	79.0	0.58	19.0	
	<b>∞ æ</b>	09.0	0.57	0.31	95.0	0.70	0.57	
LIVER	RATIO	3.78	3.83	3.60	3.71	60.4	4.01	
<b>_</b>	s 9	2.12	1.95	1.13	1.21	1.87	1.18	
	WE IGHT G.	11.53	10.28	10.27	7.88	8.70	8.43	
	ۍ د د	14	15	15	10	15	13	
BODY WEIGHT	WEIGHT G.	30 4	268 <sup>S-</sup>	285 <sup>S-</sup>	213	211	211	
8	z	12	12	12	12	12	12	
	SEX	I	I	Σ	<b>L</b>	ட	<b>L</b>	
	GROUP	~	2	m	-	7	ю	

S- = SIGNIFICANTLY LOWER THAN CONTROL

TABLE NO. 5- MEAN TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, ORGAN/BODY WEIGHT RATIOS, AND STANDARD DEVIATIONS FOR MALE AND FEMALE ALBINO RATS.

ALBINO RATS GR 2 RECEIVING WR2823 AC & GR 3 RECEIVING WR2823 AB FOR TWO WEEKS

			4	<b>3</b> 3			
	∨ <del>se</del>	6	600.0	0.004	ò		0.004
AALS	RAT 10	0.020	0.0258+	0.022	0.032	26250	0.037
ADRENALS	v <b>.</b>	0.011		0.011	0.010	0.013	0.012
	WEIGHT G.	090*0	0.068	0.063	690*0	0.070	0.078
	ν <del>se</del>	0.090	0.081	0*059	0.080	0.065	0.074
KIDNEYS	RAT 10	0.944	0.933	0.945	0.895	0.879	0.894
K IC	<b>က</b> ဖွဲ့	0.34	0.30	0.27	0.19	0.19	0.19
	WE I GHT 6.	2.87	2.50 <sup>S-</sup>	2.70	1.90	1.86	1.88
	<b>တ</b> ဖိ	14	15	15	10	15	13
BODY WEIGHT	WEI GHT G.	30 4	268 <sup>S-</sup>	285 <sup>S-</sup>	213	211	211
Ď	Z	12	12	12	12	12	12
i	X X X	I	¥	I	ιL	iL	u.
3	NUMBER	-	~	M	-	~	e.

S- = SIGNIFICANTLY LOWER THAN CONTROL S+ = SIGNIFICANTLY HIGHER THAN CONTROL

TABLE NO. 5- MEAN TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, ORGAN/BODY WEIGHT RATIOS, AND STANDARD DEVIATIONS FOR MALE AND FEMALE ALBINO RATS.

ALBIND RATS GR 2 RECEIVING WR2823 AC & GR 3 RECEIVING WR2823 AB FOR TWO WEEKS

			43	4			
	ν <del>»</del> ε				.0106	1,0067	.0058
IES	RATIO %				0.0577	0.0566 0.0067	0.0582 0.0058
DVARIES	v <b>.</b>				.023	.017	• 016
	WЕ1 GHT G•				0.123 0	$0.120\frac{11}{0.017}$	0.123 0.016
	N 96	0.11	0.15	0.10			
TESTES	RAT10	1.46	1.53	1.49			
TES	ა <b>ა</b>	0.29	0.43	0.26			
	WE IGHT G•	4.43 0.29	4.08 <sup>S-</sup> 0.43	4.23 0.26			•
	v 5	14	15	15	10	15	13
BODY WEIGHT	WEIGHT G.	30.4	268 <sup>S-</sup>	285 S-	213	211	211
90	Z	12	12	12	12	12	12
	SEX	Σ	Σ	Σ	щ	ıL	ш
	GROUP NUMBER	-	2	m	1	7	M

S- \* SIGNIFICANTLY LOWER THAN CONTROL / \* MEAN FOR NUMBER DESIGNATED

N = No Section

X = Not Remarkable

A = Autolysis

P or ✓ = Present or Taken

0 = Absent

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderate to Severe

5 = Severe

IT = Insufficient Tissue

	ı——						GROU	MALE JP NU		R					
			1					2		-			3		
AN IMAL SUADAO NUMBER	86-566	86-567	86-568	86-569	86-570	86-590	86-591	86-592	86-593	86-594	86-614	86-615	86-616	86-617	86-618
URGANS															
SPINAL CORD Extracellular Vacuolation	P	P	P	X	N	X	X	X	X	X	x	X	P	X	N
BRAIN Glial Nodules Perivascular Lymphoid Cuffing Nonsuppurative Meningitis Extracellular Vacuolation	P	P	P	P	X	x	P	X	P 1	P 1 1	X	x	P	X	X
PITUITARY	x	X	N	N	x	N	x	x	x	X	x	x	x	x	x
THYROID Level of Activity Epithelial Heighth Follicular Size		3 2-3 2-3		IT	3 2-3 2-3	2 4		3-4 3-4 2-3	3 3 3	3 2-3 2-3	IT	3 3 2-3	4 4 2-3	3 2 4	3 3 2-1
ADRENAL Vacuolation of Zona Fasciculata	1	1	1	1	1	2		1	1	1	1	1	1	1	1
HEART Epicarditis Focal Myocarditis Valvulitis	1	X	х	X	X	X	x	2	1	1 1 1	1	1	1	1	1
LUNG Peribronchial Lymphoid Hyperplasia			2											1	
Perivascular Lymphoid Infiltration Interstitial Pneumonitis	2	2	2	3 5	3	1	1	2 2	2	1	1	2 2	3	2 1	2 1
LIVER Nonsuppurative Hepatitis Pericholangitis	х	x		X	x	X	x	1	2	2 2	X	x	x	X	2
KIDNEY Epithelial Hyperplasia Interstitial Nephritis Regenerative Epithelium Pyelitis	X	x	X	X	x	1	x	1	1 1 1	1	X	x	x	x	1 2
PANCREAS Pancreatitis	х	x	x	x	x	x	1	1	1	x	X	x	X	x	x

						M	ALES		NTIN						
							GROU	JP NI	IMBEI	3					
		1 (C	nti	ıed			2 (C	ontir	ued			3 (C	onti	ued)	
AN I WAL SURGER SURGER	86-566	86-567	895-98	86-569	86-570	86-590	86-591	86-592	86-593	86-594	86-614	86-615	86-616	86-617	86-618
TESTIS Nonsuppurative Epididymitis	1	X	1	X	X	X	1	X	1	1	1	X	1	1	X
PROSTATE Prostatitis	х	x	x	X	X	X	X	x	x	x	x	x	X	2	x
URINARY BLADDER Artifact	х	x	x		X	x	x	x	P	X	x	x	x	x	x
BONE MARROW															
Hematogenic Activity	3	3	3	4	4	3	3	3	3	4	3	2	2	2	2
Number of Megakaryocytes	3	3	3	4 3	4 3	3 3	3 3	3 3	3	4 3	3 3	3 3	3 3	3	3
Number of Erythroid and		•	•	-	•	•	•	•	•	•	,	,	,	,	3
Myeloid Cells	5	3	3	3	3	3	3	3	3	3	3	3	3	3	3
INJECTION SITE (TAIL)							N								
Focal Inflammation in Derma	P	P	P	P	P	P		P	P	P	P		P	P	P

	ı <del></del>							EMAL P NI	es Mber		<del></del>	-		<del></del>	
			1					2					3		
AN I WAL	86-578	86-579	86-580	86-581	86-596	86-602	86-603	86-604	86-605	86-613	86-626	86-627	86-628	86-629	86-630
SPINAL CORD	х	N	х	x	<del></del> +	х	х	x	х	×	х	x	х	x	<u>x</u>
Extracellular Vacuolation															
BRAIN Glial Nodules Perivascular Lymphoid Cuffing Nonsuppurative Meningitis Extracellular Vacuolation	x	N	X	P 1 1	1 P	X	X	X	P 1 1	x	X	X	X	X	P
PITUITARY	x	N	N	X	X	X	N	X	X	N	X	N	X	X	X
THYROID  Level of Activity  Epithelial Heighth  Follicular Size	3 2 2-3	N	N	2 2 2-3	3 3 2-3	3 2-3 2-3	3 3 2-3	3 3 2-3	3 3 2-3	N	3 3 2-3	N	N	3 3 2-3	3 3 2-
EYE Harderian Adenitis	х	X	X	X	x	N	X	P	X	P	X	N	X	X	X
HEART Epicarditis Focal Myocarditis Valvulitis	1	X	x	1 1 1	1	X	X	X	1	1	X	x	X	1	х
LUNG Peribronchial Lymphoid Hyperplasia		1		1		2	1	2	1	1	2	2	1	1	2
Perivascular Lymphoid Infiltration Interstitial Pneumonitis	1 1	1	2	2	2 1	3	1	2 2	3 2	3 2	1	2	1	3	2 1
LIVER Nonsuppurative Hepatitis Pericholangitis	2	x	1	1 2	x	x	x	x	1	1	x	-	х	1	x
KIDNEY Interstitial Nephritis Regenerative Epithelium	X	x	x	x	x	1	1	x	x	x	1	x	x	1	x
PANCREAS Pancreatitis	x	x	x	1	x	X	x	x	1	x	1	x	x	x	x

	ſ						FE		S (C		NUET R	<u>,                                     </u>				
	ţ		1 (C	onti	nued		2		ntin		_	3	(Ço	ntin	ued)	
ORGANS	AN IMAL NUMBER	86-578	86-579	86-580	86-581	86-596	86-602	86-603	86-604	86-605	86-613	86-626	86-627	86-628	86-629	86-630
URINARY BLADDER Mucosal Epithelial Vacuola	tion	х	х	х	х	х	х	х	х	х	х	N	N P	х	x	х
BONE MARROW Hematogenic Activity		4	4	4	4	4	3	3	4	3	3	4	3	4	3	3
Number of Megakaryocytes Number of Erythroid and Myeloid Cells		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
INJECTION SITE (TAIL) Focal Inflammation in Derma	a	P	P	P	P	P	P	N	P	P	P		P	p	P	P

TRW/

# HAZLETON LABORATORIES

SPONSOR: Walter Reed Army Institute of Research

DATE: July 6, 1971

MATERIAL: WR 149,024 AD (AX 67287)

LOT NO: 308/422

SUBJECT:

REPORT NO. 39

Acute Intravenous Toxicity Study - Rats and Mice Acute Intraperitoneal Toxicity Study - Guinea Pigs

Project No. 193-413

#### SUMMARY

WR 149,024 AD (AX 67287) was evaluated for acute intravenous toxicity in male albino rats and mice and for acute intraperitoneal toxicity in male albino guinea pigs. The acute intravenous LD50 in rats is 41.7 mg/kg of body weight (confidence limits, 39.3 to 44.2 mg/kg) and in mice is 35.5 mg/kg of body weight (no confidence limits due to all-or-none response). The acute intraperitoneal LD50 in guinea pigs is 204 mg/kg of body weight (confidence limits, 169 to 247 mg/kg).

Test Material WR 149,024 AD (AX 67287); Lot No: 308/422.

#### Procedures

Animals: Seven groups for each species, each composed of 10 males. Rats weighed from 89 to 175 grams, mice from 20 to 37 grams. and guinea pigs from 325 to 530 grams at initiation.

Drug Administration: By intravenous injection via the lateral tail vein in the rats and mice, and by intraperitoneal injection in the guinea pigs. Concentrations were adjusted so that mice were dosed with a total volume of 10 ml. of compound and vehicle per kg. of body weight. Rats and guinea pigs were dosed with a total volume of five ml. of compound and vehicle per kg. of body weight. The vehicle, normal saline, was administered to control animals in volumes equal to those for their respective test groups.

## Dosage Levels:

Mice - 10.0, 15.9, 20.0, 25.1, 31.6, and 39.8 mg/kg of body weight.

Rats - 25.1, 31.6, 39.8, 44.7, 50.1, and 63.1 mg/kg of body weight.

Guinea Pigs - 25.1, 39.8, 63.1, 100, 159, and 251 mg/kg of body weight.

- Observations: For mortality and pharmacotoxic effect immediately after dosing, frequently on the day of dosing, and daily thereafter, for a total of 14 days. Gross necropsies were performed on all animals which died or were sacrificed at termination.
- Statistical Analysis: Mortality data were analyzed by the method of Litchfield, J. T., and Wilcoxon, F., J. Pharmacol. Exptl. Therap. 96, 99, 1949.

#### Results

Mortality Data: Values below represent the number of animals dead per number of animals tested, cumulative.

# HAZLETON LABORATORIES

		Ti	me of Death -	Mice
Dose	Concentration	Immediate	Hours	Days
mg/kg	<b>9</b> 5		24	2 - 14
10.0	0.10	0/10	0/10	0/10
15.9	0.16	0/10	0/10	0/10
20.0	0.20	0/10	0/10	0/10
25.1	0.25	0/10	0/10	0/10
31.6	0.32	0/10	0/10	0/10
39.8	0.40	10/10		

LD<sub>50</sub>, mg/kg - 35.5 (No confidence limits due to all-or-none response.)

		Ti	me of Death -	Rats
Dose mg/kg	Concentration %	Immediate	Hours 24	Days 2 - 14
mR\ v-R	79		24	2 - 14
25.1	0.50	0/10	0/10	0/10
31.6	0.63	0/10	o/10	0/10
39.8	0.80	1/10	1/10	1/10
44.7	0.89	9/10	9/10	9/10
50.1	1.0	10/10		
63.1	1.3	10/10		

LD<sub>50</sub>, mg/kg - 41.7 Confidence Limits (95%), mg/kg - 39.3 to 44.2 Slope - 1.116

Graphical presentation of the dose-response evaluations is appended to this report.

#### HAZLETON LABORATORIES

		Tin	me of Death -	- Guinea	Pigs	
Dose	Concentration	Immediate	Hours		Days	
mg/kg	9,		24	2-9	10	11-14
25.1	2.5	0/10	0/10	0/10	2/10	2/10*
39.8	4.0	0/10	0/10	0/10	1/10	1/10*
63.1	6.3	0/10	0/10	0/10	0/10	0/10
100	10.0	0/10	0/10	0/10	0/10	0/10
159	15.9	0/10	1/10	1/10	1/10	1/10
251	25.1	0/10	8/10	8/10	8/10	8/10

 $LD_{50}$ , mg/kg - 204 Confidence Limits, (95%), mg/kg - 169 to 247 Slope - 1.375

Graphical presentation of the dose-response evaluation is appended to this report.

\* Death considered due to spontaneous causes; not included in calculation of  ${\rm L}\Gamma_{50}$ .

#### Frincipal Toxic Effects:

Following Intravenous Injection in Mice - Sores were observed on the tails of nine control mice from Day 7 through Day 14. Slight depression was noted in all mice from Groups No. 5 (25.1 mg/kg) and No. 6 (31.6 mg/kg) immediately after dosing.

Following Intravenous Injection in Rats - Fecal stains were observed on from one to four rats from Group No. 2 (25.1 mg/kg) from Day 6 through Day 14, and on from one to three rats from Group No. 4 (39.8 mg/kg) from Day 5 through Day 14. One Group No. 5 (44.7 mg/kg) rat showed fecal stains on Day 5. Slight depression

was seen within 30 minutes postdose and for the remainder of the day in all rats from Group No. 3 (31.6 mg/kg) and in eight Group No. 4 rats. One Group No. 5 rat was slightly depressed on Day 1. Ten Group No. 3 rats and eight Group No. 4 rats exhibited decreased activity, limb weakness, and irregular respiration immediately after dosing, and one Group No. 5 rat showed prostration, momentary lapses of respiration (apnea), and decreased activity immediately after dosing. All Group No. 3 rats lost the righting reflex and were ataxic immediately after dosing. Decreased activity and irregular respiration were noted within 30 minutes postdose and for the remainder of the day in one Group No. 5 rat.

Following Intraperitoneal Injection in Guinea Pigs - One Group No. 2

(25.1 mg/kg) animal exhibited irregular respiration on Day 1 and labored respiration on Day 6, Day 7, and Day 9. One Group No. 2 animal showed alopecia, ataxia, thinness, sneezing, and nasal discharge on Day 8 and Day 9. One or two Group No. 3 (39.8 mg/kg) animals showed the following signs from Day 5 or Day 6 through Day 8 or Day 9: slight depression, alopecia, anorexia, nasal discharge, hunched posture, and emaciation. One Group No. 3 animal also showed alopecia from Day 12 through Day 14, and another Group No. 3 animal exhibited ptosis, with exudate from one eye on Day 5.

Major Necropsy Findings:

Following Intravenous Injection in Mice - One Group No. 3 (15.9 mg/kg) mouse exhibited a lesion on the liver following sacrifice.

Following Intravenous Injection in Rats - No gross pathology was noted at death or sacrifice.

Following Intraperitoneal Injection in Guinea Pigs - One Group No. 6 (159 mg/kg) guinea pig showed pale tan kidneys at sacrifice.

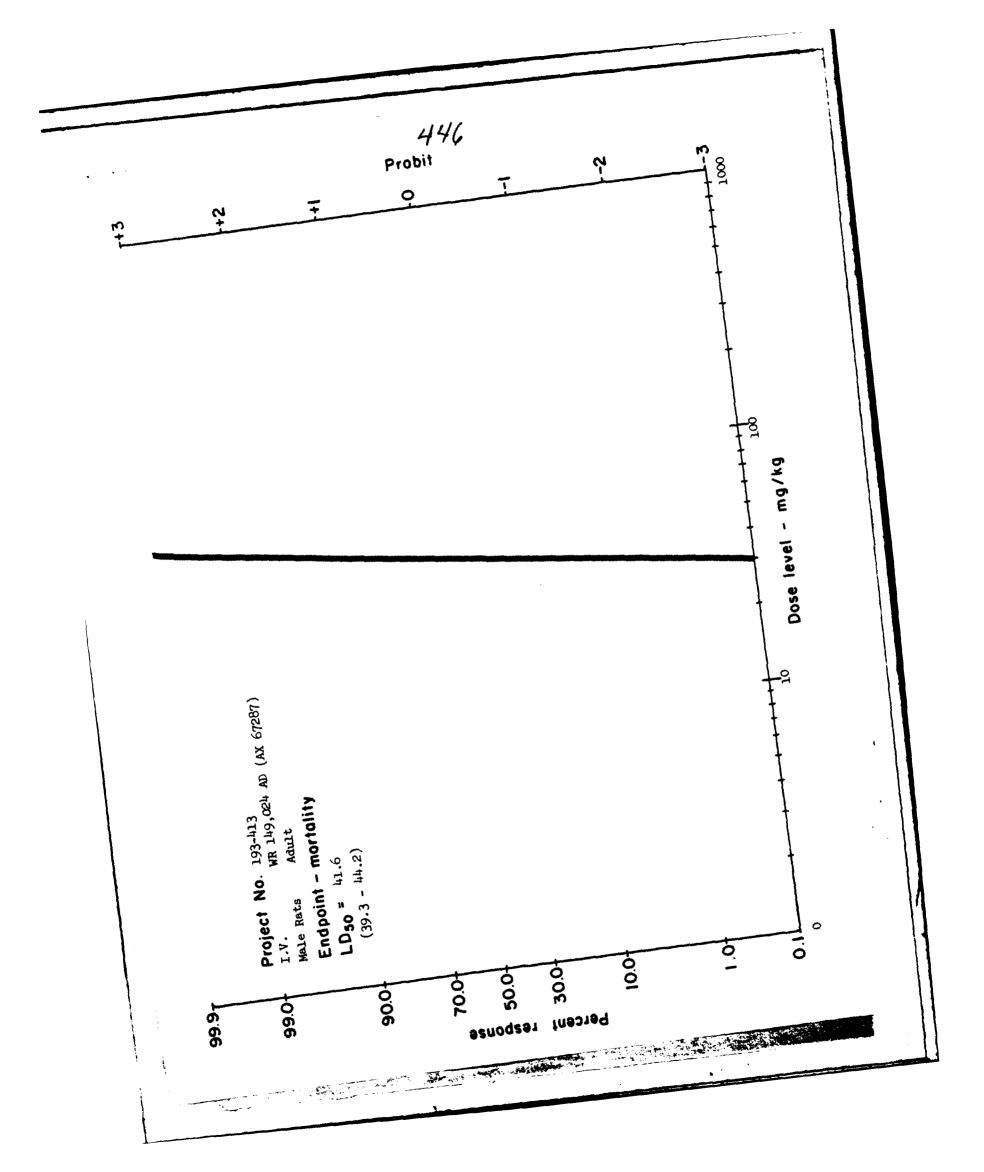
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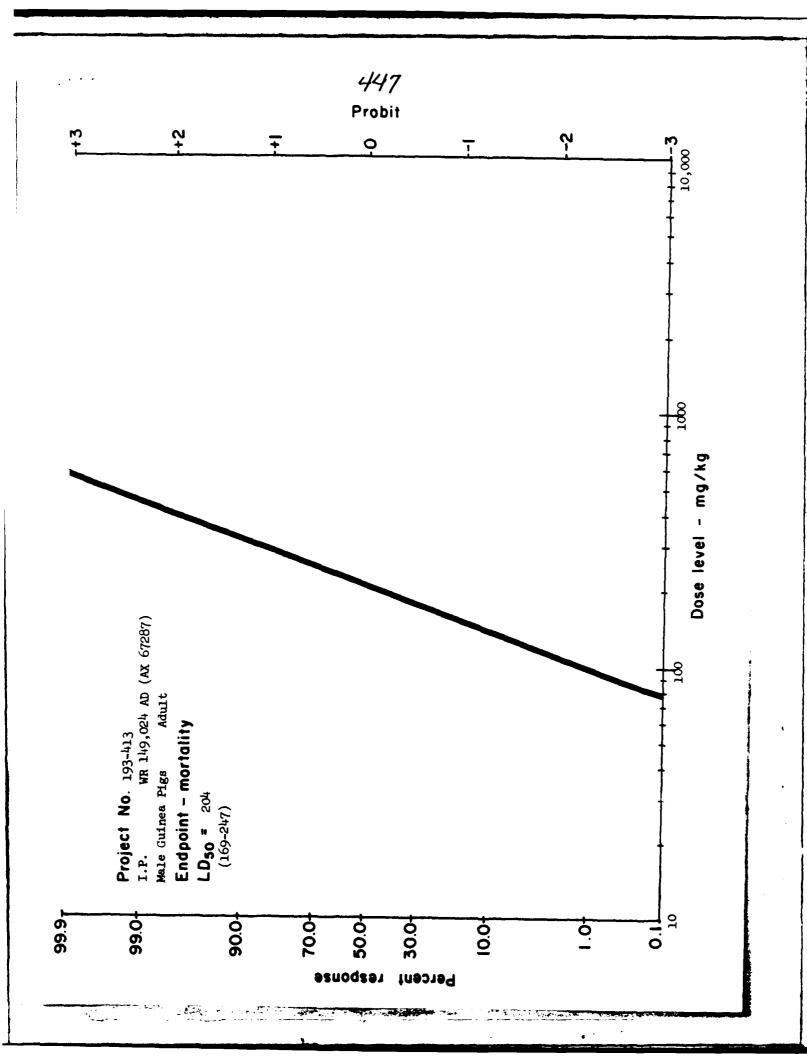
FREDERICK E. RENO, Ph.D.
Project Manager, Drugs and
Industrial Chemicals Department
Toxicology-Biosciences Laboratory

Report Preparation: Spruill

Supervision: Minner

sad





TRW/

HAZLETON LABORATORIES

SPONSOR:

Walter Reed Army Institute of Research

DATE: September 15, 1971

MATERIAL:

WR 149,024 AD (AX 67287)

LOT NO: 308/422

SUBJECT:

REPORT NO. 41

Acute Intravenous Toxicity Study - Dogs

Project No. 193-414

#### SUMMARY

WR 149,024 AD was evaluated for acute intravenous toxicity in male purebred beagles at seven dosage levels ranging from 3.2 to 150 mg/kg of body weight. Observations for toxic and/or pharmacologic effect were recorded for seven days postdose, at which time the surviving animals were sacrificed. Representative tissues were preserved and sections of liver and kidneys were examined microscopically from each animal sacrificed at termination.

Dosage levels of 150 and 75 mg/kg produced death within three minutes postdose in the single animal treated at each level. Immediate respiratory arrest, cyanosis, rapid heart rates, salivation, retching, and cutaneous twitching were observed prior to death. Dose-related signs observed at the five lower dosage levels tested (37.5, 18.75, 9.38, 4.69, and 3.2 mg/kg) included rapid heart rates, deepened or depressed respiratory activity, pink or reddened mucous membranes, retching, emesis, quivering, pupillary dilation, salivation, temporary absence of reflexes, and cyanosis. Each of the animals at the five lower dosage levels recovered.

Gross Pathology and microscopic examination of sections of liver and kidney for the animals sacrificed at termination revealed no compound-related alterations.

Therefore, the maximum nonlethal dose level tested was 37.5 mg/kg.

#### OBJECTIVE

The purpose of this study was to evaluate the toxicity of WR 149,024 AD (AX 67287) following a single intravenous dose to adult purebred beagles.

#### MATERIAL

Identification WR 149,024 AD (AX 67287); Lot No. 308/422.

Description A white powder with a faint odor.

Receipt Date May 12, 1971.

Purity Assumed 100% active ingredient.

#### **METHODS**

# Experimental Animals

Breed: Young adult purebred beagles.

Number: Seven males.

Body Weight Range: At initiation from 9.3 to 14.5 kg.

Housing: Individually in metal cages.

Diet: Ground Wayne Dog Meal and water ad libitum.



## Groups and Dosage Levels

Group No.	No. of Animals	Dosage Level mg/kg
1	1	3.20
2	1	4.69
3	1	9.38
4	1	18.75
5	1	37.50
6	1	75.00
7	1	150.00

## Compound Administration and Preparation

The test material was mixed with isotonic saline at a concentration of 500 mg/ml and injected once at the specificed dose levels into the cephalic vein of the forepaw at a rate of 0.1 ml. per 10 seconds.

## Observations and Records

Mortality and Toxic Effects: Immediately, frequently on the day of dosing and daily thereafter for seven days.

Body Weights: Initially and terminally.

## Terminal Studies

Terminal Sacrifice: By exsanguination under Surital anesthesia after a seven-day observation period.

Gross Necropsy: Performed on all animals sacrificed at termination.

Tissue Preservation: The following tissues from each animal sacrificed at termination were preserved in 10% neutral buffered formalin: brain, pituitary, thoracic spinal cord, eye, thyroids, lung, heart, liver (two lobes), gallbladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, prostate, skin, rib junction, bone marrow, and nerve with muscle.

The testes with epididymis were preserved in Bouin's fixative.

## Histopathological Examination

One section from each of two lobes of the liver and three sections from the kidneys were examined microscopically from each animal sacrific we at termination.

#### RESULTS

Appearance, Behavior, Body Weight Changes, and Signs of Compound Effect
Individual body weights and compound administration are presented
in Table No. 1.

3.2 mg/kg Level: The predose heart rate of 108/minute reached a peak of 172/minute at one minute postdose. The predose respiratory rate of 32/minute reached a peak of 36/minute at one minute postdose. Recovery to predose levels occurred three minutes postdose, and the animal appeared normal.

- 4.69 mg/kg Level: The predose heart rate of 132/minute reached 192/minute immediately postdose. Respiration was slightly deepened only.
  Approximately one and one-half hours postdose the animal appeared normal.
- 9.38 mg/kg Level: The predose heart rate of 96/minute reached 204/minute immediately postdose. By two minutes postdose, retching with mucoid emesis, rapid and pronounced respiratory contractions, and pink mucous membranes were observed. Five minutes postdose, and the animal appeared sedated but normal.
- 18.75 mg/kg Level: Depressed respiration, diaphragmatic contractions, reddened mucous membranes and a change from a predose heart rate of 54/minute to 190/minute were observed immediately postdose. Retching, mucoid emesis, and fully dilated pupils at three minutes and slight quivering at 18 minutes were also observed. By 24 hours, the animal appeared normal.
- 37.5 mg/kg Level: Approximately 30 seconds postdose the animal went down as if under anesthesia and was salivating slightly; by two minutes the toe-pinch reflex was absent and did not recover until 17 minutes. The predose heart rate of 108/minute increased to 240/minute at two minutes postdose. Retching (no emesis), deep and slightly irregular respiration, dilated pupils, and slight cyanosis were also observed at this time. By seven minutes postdose, respiration was normal and cyanosis was disappearing. By 24 hours, the animal appeared normal.

75 and 150 mg/kg Levels: Respiratory arrest, cyanosis, salivation and retching or cutaneous twitching, and increased heart rates preceded death at three minutes postdose in both animals.

#### Gross Pathology

- 18.75 mg/kg Level: The heart muscle appeared hard (Dog No. 15357).
- 37.5 mg/kg Level: A cyst was observed at the base of the pituitary (Dog No. 15405).

No gross alterations were observed among any of the other test animals which were sacrificed following the seven-day observation period.

## Microscopic Pathology

Representative sections of liver and kidney were evaluated microscopically from Dogs No. 15400 (3.2 mg/kg), No. 15399 (4.69 mg/kg), No. 15376 (9.38 mg/kg), No. 15357 (18.75 mg/kg), and No. 15405 (37.5 mg/kg).

Incidental findings included hepatic mononuclear cell infiltration and chronic interstitial nephritis.

HAZLETON LABORATORIES

No significant pathological alterations were detected which could be attributed to the test material.

Submitted by

FREDERICK E. RENO, Ph.D.
Project Manager, Drugs and
Industrial Chemicals Departmen

Industrial Chemicals Department Toxicology-Biosciences Laboratory

Pathology by

JON F. FERRELL, D.V.M. Consultant Pathologist

Report Preparation: Horwatt

Supervision: Upman

gbb

NOTE: The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

Table No. 1 - Individual body weights and compound administration for male purebred beagles which received a single intravenous injection of WR 149,024 AD (AX 67287)

	3.3	9	7	60	o	0 36 0	DOSE LEVEL - MG/KG	L - MG/K		27 E	37			-
							100 100	OG NO.	}					130.0
TIME	15	5400	15	399	15	376	15	357	15	405	152	1265		15252
INTERVAL	VT.	Mg. kg.	WT.	CPD.	kg.	CPD.	kg.	CPD.	WT.	GPD.	WT.	CPD.	<i></i>	MT.
Initial	9.6	98	30 11.8	55	9.5	87	11.3	210	10.6	395	14.5	1080		13.7
Terminal*	9.1		11.6		9.1		11.2		10.2		*			*
Net Change, kg.	-0.3		-0.2		-0.2		-0.1	٠	4.0-					

\* Terminal weights are fasted weights

\*\* Death occurred three minutes postdose

# HISTOPATHOLOGICAL EVALUATION OF MALE PUREBRED BEAGLES SACRIFICED AT TERMINATION

**GROSS** 

MICROSCOPIC

GROUP NO. 1 - 3.2 MG/KG Male Dog No. 15400

Liver:

No alterations observed.

Minimal focal mononuclear cell infiltration.

The following organ was not altered grossly or microscopically: kidney.

GROUP NO. 2 - 4.69 MG/KG Male Dog No. 15399

Kidney:

No alterations observed.

Minimal focal chronic interstitial nephritis.

The following organ was not altered grossly or microscopically: liver.

GROUP NO. 3 - 9.38 MG/KG Male Dog No. 15376

The following organs were not altered grossly or microscopically: liver and kidney.

GROUP NO. 4 - 18.75 MG/KG Male Dog No. 15357

The following organs were not altered grossly or microscopically: liver and kidney.

GROUP NO. 5 - 37.5 MG/KG Male Dog No. 15405

Liver:

No alterations observed.

Minimal focal mononuclear cell infiltration.

The following organ was not altered grossly or microscopically: kidney.

	,					MALES		······
	ŀ	3.2	4.69	9.38	DOSE 1 18.75	EVEL - MG 37.5	/KG	
		J. 2	4.03	3.30	10.75	<u> </u>		
	MAL	8	6	92	57	59		
	ANTMAL NUMBER	15400	15399	15376	15357	15405		
organs			<u> </u>	İ	L	<u></u>	<del></del>	<del></del>
	}							
LIVER		_	X	X	X			
Mononculear Infiltratio	on (	1				1		
KIDNEY	ĺ	X	_	x	X	X		
Interstitial Nephritis			1					
	İ							
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	l							
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TRW/

HAZLETON LABORATORIES

SPONSOR: Wa

Walter Reed Army Institute of Research

DATE: September 7, 1971

MATERIAL:

WR 149,024 AD (AX 67287)

LOT NO: 308/422

SUBJECT:

REPORT NO. 40

Acute Intravenous Toxicity Study - Monkeys

Project No. 193-415

#### SUMMARY

WR 149,024 AD was evaluated for acute intravenous toxicity in male rhesus monkeys at six dosage levels ranging from 9.38 to 150.0 mg/kg of body weight. Observations for toxic and/or pharmacologic effect were recorded for seven days postdose, at which time the surviving animals were sacrificed. Representative tissues were preserved from all dead or sacrificed monkeys, and sections of liver and kidneys were examined microscopically from each animal.

Dosage levels of 150 and 75 mg/kg produced immediate death in the single animal treated at each level. The animal given 56.25 mg/kg developed shallow or temporary cessation of respiratory activity, but recovered. Two animals treated with 37.5 mg/kg showed rapid heart rates and respiration, but also recovered. No noticeable pharmacologic effects were observed at 18.75 or 9.38 mg/kg.

Microscopic examination of sections of liver and kidney revealed no consistent dosage-related alterations.

Therefore, the maximum nonlethal dose level tested was 56.25 mg/kg.

#### OBJECTIVE

The purpose of this study was to evaluate the toxicity of WR 149, 024 AD (AX 67287) following a single intravenous dose to adult male monkeys.

#### MATERIAL

<u>Identification</u> WR 149,024 AD (AX 67287); Lot No. 308/422.

Description White powder.

Receipt Date May 12, 1971.

Purity Assumed 100% active ingredient.

#### METHODS

## Experimental Animals

Breed: Young rhesus monkeys.

Number: Eight males.

Body Weight: At initiation from 1.8 to 3.5 kg.

Housing: Individually in metal cages.

Diet: Purina Monkey Chow twice daily, fresh fruit daily, and water ad

libitum.

# HAZLETON LABORATORIES

## Groups and Dosage Levels

Group No.	No. of Animals	Dosage Level mg/kg
1	1	9.38
2	2	18.75
3	2	37.50
4	1	56.25
5	1	75.00
6	1	150.00

#### Compound Administration and Preparation

The test material was mixed with isotonic saline at a concentration of 300 mg/ml and injected once at the specified dose levels into the saphenous vein of the hindlimb at a rate of 0.1 ml. per 10 seconds.

## Observations and Records

Daily: Appearance, behavior, appetite and elimination, and pharmacotoxic signs.

Initially and Terminally: Body weight.

## Terminal Studies

Terminal Sacrifice: By exsanguination under anesthesia after seven days.

Gross Necropsies: On all sacrificed monkeys.

#### Tissues Preservation:

In 10% Neutral Buffered Formalin - Brain, pituitary, thoracic spinal cord, eye, thyroids, lung, heart, liver (two lobes), gallbladder,



spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, prostate, testes, skin, rib junction, bone marrow, nerve with muscle, and unusual lesions.

## Microscopic Examination

The following tissues were examined from all animals: liver (one section from two lobes) and kidneys (three sections).

#### RESULTS

# Appearance, Behavior, Body Weight Changes, and Signs of Compound Effect

Individual body weights and amounts of compound administered are presented in Table No. 1.

No apparent effects were observed in animals dosed at 9.38 and 18.75 mg/kg.

At two minutes postdose, Monkeys No. 825H and No. 823H (37.5 mg/kg levels) showed rapid heart rates, rapid or deep breathing, and were down in their cages. Recovery occurred four or six minutes postdose.

Labored and shallow respiration and faint, slow heart rate preceded a temporary cessation of respiration at two minutes postdose in Monkey

No. 824H (56.25 mg/kg level). Recovery occurred at 11 minutes postdose.

Respiratory paralysis immediately postdose preceded death in Monkeys No. 821H and No. 820H (75 mg/kg and 150 mg/kg, respectively).

## Gross Pathology

The stomach mucosa of Monkey No. 823H (37.5 mg/kg level) appeared reddened.

An encapsulated area attached to the left kidney of Monkey No. 828H was taken for microscopic analysis. The cut surface revealed a brown exudate and several small worms.

Signs of parasitic infestation (Monkey No. 828H) and adhesions of lungs to pleura (Monkey No. 827H) are commonly-occurring signs in monkeys and are considered incidental to the administration of the test compound.

#### Microscopic Pathology

No consistent, dosage-related alterations were observed in the sections examined which could be attributed to the test compound. Occasional collections of cells in the form of focal mononuclear infiltration or pericholangitis were seen in most sections of liver. Subacute pericholangitis was observed in Monkey No. 925H. However, the liver parenchyma was within normal limits, and the liver sections from the other animal at the same dose level (Monkey No. 823H) were considered not remarkable.

Minimal to mild interstitial nephritis was present in kidney sections from all animals and was not considered to be related to the test procedure.

Mild edema and pyelitis were present in one animal treated at 37.5 mg/kg. However, this change was not seen in the other animal at the same dosage nor in the highest level animal.

A section of stomach from Monkey No. 823H appeared to be within normal limits.

In conclusion, no consistent pathological alterations were detected in the sections examined which could be attributed to the test compound.

Submitted by

FREDERICK E. RENO, Ph.D.
Project Manager, Drugs and
Industrial Chemicals Department
Toxicology-Biosciences Laboratory

Pathology by

JOHN F. FERRELL, D.V.M. Consultant Pathologist

Report Preparation: Horwatt Supervision: R. Thompson

gbb

NOTE: The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

Table No. 1 - Body weights and compound consumption for male rhesus monkeys

	820Н	WT. CPD. WT. CPD.	0.066 9.	ند	t
		8 . kg	.0 2.	*	,
	821H	CP	8 135		
		돌 3	٦.	*	1
	324H	CPD.	163.1		
	_	K 8	2.9	3.0	+0.1
02	323H	CPD.	97.5		
MONKEY NO.		K 8.	2.6	2.7	+0.1
-24	325H	CPD.	91.0		
		K 8	2.4	2.5	+0.1
	H7 61	CPD.	0.09		
		Kg.	3.2	3.0	-0.2
	1961	CPD.	58.1		
				3.0	-0.1
	noco	WT. CPD.	3.5 17.8		
	1			** 3.8	ge, -0.3
	ante.	INTERVAL	Initial	Terminal** 3.8	Net Change, kg0.

\* Not available

\*\* Terminal weights are fasted weights

## HISTOPATHOLOGICAL EVALUATION OF MONKEYS

GROSS

MICROSCOPIC

Animal No. 828H 9.38 mg/kg

# Liver:

No abnormalities observed. Minimal focal mononuclear cell infiltration.

# Kidney:

Encapsulated area attached to left kidney. Cut surface revealed brownish exudate and several small worms.

Parasitic nodules were sæn throughout the mesentary.

There was an occasional minimal focus of chronic interstitial nephritis within the kidney parenchyma.

There was a prominent granulomatous reaction containing nematode parasites on the capsular surface of the kidney.

MICROSCOPIC

Animal No. 826H 18.75 mg/kg

Liver:

No abnormalities observed.

Minimal focal mononuclear cell

infiltration.

Kidney:

No abnormalities observed.

Slight chronic interstitial

nephritis.

MICROSCOPIC

Animal No. 827H 18.75 mg/kg

Liver:

No abnormalities observed.

Minimal focal mononuclear cell

infiltration.

Kidney:

No abnormalities observed.

Minimal focal chronic interstitial

nephritis.

MICROSCOPIC

Animal No. 823H 37.5 mg/kg

Liver:

No abnormalities observed.

Not remarkable.

Kidney:

No abnormalities observed.

Minimal chronic interstitial nephritis.

There was also a mild mononuclear cell infiltration and looseness of the tissue due apparently to edema in the area of the pelvis.

Stomach:

Mucosa appeared slightly reddened.

The tissue appeared to be within normal limits.

MICROSCOPIC

Animal No. 825H 37.5 mg/kg

Liver:

No abnormalities observed. Mild pericholangitis characterized by accumulations of neutrophils and mononuclear inflammatory cells in the areas surrounding the bile ducts.

Kidney:

No abnormalities observed. Minimal focal chronic interstitial nephritis.

MICROSCOPIC

Animal No. 824H 56.25 mg/kg

Liver:

No abnormalities observed.

Minimal nonsuppurative peri-

cholangitis.

Kidney:

No abnormalities observed.

Slight focal chronic interstitial

nephritis.

# KEY FOR INCIDENCE TABLE

P = Present

NS = No Section

X = Not Remarkable

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderately Severe/High

5 = Severe/High

# DETAILED HISTOPATHOLOGY INCIDENCE TABLE

	d	D	ose Le	vel-mg	/kg	
	8	9.38	18.75	37.5	56.25	
	Animal	828H	826H 827H	823H 825H	824H	
SEX		M	мм	мм	M	
LIVER				x		
Mononuclear cell infiltration Pericholangitis		1	1 1	2	1	
KIDNEY						
Parasitic granuloma Interstitial nephritis Edema Pyelitis		P 1	2 1	1 1 2 2	2	
STOMACH				x		

TRW/

# HAZLETON LABORATORIES

SPONSOR:

Walter Reed Army Institute of Research

DATE: September 27, 1971

MATERIAL:

WR 149,024 AD (AX 67287)

LOT NO: 308/422

SUBJECT:

REPORT NO. 42

Subacute Intravenous Toxicity - Dogs

Project No. 193-416

#### SUMMARY

WR 149,024 AD (AX 67287) was tested for subacute (two weeks) intravenous toxicity in dogs by injections into the cephalic vein of the forelimb once daily, seven days a week, for two weeks, at dosage levels of 5, 10, and 20 mg/kg.

Postdose tachycardia, slight at the low level and increasing to moderate at the high level with recovery by two minutes postdose, and emesis were observed among all treated animals. Mydriasis, panting, and ataxia were also observed at the high level.

Analysis of clinical data and ophthalmoscopic examinations revealed no compound-induced alterations. Gross necropsy and inspection of organ/body weight data revealed no conclusive evidence of compound effect.

Microscopic examination of selected tissues revealed an increase in the amount of parafollicular tissue in the thyroids of the intermediate and high level females. This was not observed in the low level females or in any of the males. All other tissues examined failed to show an indication of compound-related effects.

#### **OBJECTIVE**

The purpose of this study was to evaluate the toxicity of WR 149,024 AD (AX 67287) following intravenous injection daily seven days a week for two weeks.

#### MATERIAL

<u>Identification</u> WR 149,024 AD (AX 67287); Lot No. 308/422.

Description White powder.

Receipt Date May 12, 1971.

Purity Assumed 100% active ingredient.

#### **METHODS**

## Experimental Animals

Breed: Young adult purebred beagles.

Number: Twelve males and 12 females.

Body Weight (At Initiation): From 8.0 to 14.4 kg. for males and 6.4 to 11.0 kg.

for females.

Housing: Individually ', elevated metal cages.

Diet: Ground Wayne Dog Meal.



#### Groups and Dosage Levels

Group No.	No. of male	Animals female	Dosage Levels mg/kg of body weight
1 (Control)	3	3	0
2	3	3	5
3	3	3	10
4	3	3	20

#### Compound Administration and Preparation

The compound was mixed with isotonic saline as a 5% solution and injected once daily, seven days a week, for two weeks, into the cephalic vein of the forelimb.

#### Observations and Records

Daily: Appearance, behavior, appetite, elimination, and pharmacotoxic signs.

Weekly: Body weight.

## Clinical Signs

Performed: Initially and at one and two weeks.

Hematology: Hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte count, and clotting time.

Clinical Biochemistry: Fasting blood sugar, blood urea nitrogen, total serum protein, total serum bilirubin, serum albumin, serum sodium, serum potassium, serum chloride, carbon dioxide, serum calcium, serum glutamic-pyruvic transaminase, serum alkaline phosphatase, serum glutamic-oxaloacetic transaminase, and serum electrophoresis.

Urine Analysis: Specific gravity, pH, glucose, ketones, total protein, bilirubin, and microscopic examination of sediment.

#### Ophthalmoscopic Examination

Performed on all dogs initially and at termination.

## Terminal Studies

Terminal Sacrifice: By exsanguination under Surital anesthesia.

Gross Necropsies: On all sacrificed dogs.

Tissue Preservation: In 10% neutral buffered formalin - Brain, pituitary, thoracic spinal cord, eye thyroids, lung, heart, liver, gallbladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, ureters, urethra, prostate, ovary, skin, rib junction, bone marrow, nerve with muscle, and arry unusual lesions.

Organ Weights: Thyroids, heart, liver, spleen, kidneys, adrenals, and testis with epididymis.

## Histopatholoical Examination

From Control and High Level Animals: Thyroids, heart, liver, gallbladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testis, ovary, and bone marrow.

From Low and Intermediate Level Animals: Liver, kidney, thyroids, and unusual lesions.



#### RESULTS

#### Appearance, Behavior, and Signs of Compound Effect

Individual weekly body weights are presented in Table No. 1.

Postdose tachycardia, slight among the low dose animals and increasing to moderate at the high dose, was observed among the treated animals. At the high dose, this was accompanied by panting, slight ataxia, reddening of the visible mucous membranes, scleral injection, and moderate mydriasis. Treated animals quickly returned to normal, however, within 15 to 20 seconds at the low dose and within two minutes at the high dose level.

Emesis following dosing was observed at least once during the study in all treated animals, with the incidence increasing to nearly daily at the high level. This was accompanied by salivation among two or three animals at the intermediate and high level.

Control animals appeared normal throughout the study.

Body weight losses of 7% to 8% of the initial weight were observed for high level animals. The remaining animals either gained or maintained ( $\pm$  5%) of body weight.

#### Clinical Studies

The results of the clinical studies on individual animals are presented in Tables No. 2 (hematology), No. 3 (blood chemistry), and No. 4 (urine analysis).

Clinical data revealed no consistent trends that could be attributable to the administration of the compound. A slight decrease in red blood cell values were observed in one or two animals of each sex at one and two weeks. Incidental variations were seen in one or two animals in control or test groups, and by themselves did not constitute trends.

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#### Ophthalmoscopic Examination

Eye examinations were performed on all dogs initially and at the termination of the study using Mydriacyl as a mydriatic, a binocular magnifier, and a binocular indirect ophthalmoscope.

No compound-related ocular lesions were evident. Incidental changes which were present in two control dogs initially were also seen at terminal examination and are listed below.

Male Dog No. 15398: Prominent vitreous strand, both eyes; hypertrophy of Harders' gland, right eye.

Female Dog No. 15319: No tapetum lucidum present, both eyes.

The eyes of the remaining 22 dogs on the study appeared grossly normal.

#### Major Necropsy Findings

No compound-related alterations were found at necropsy. Dark pink or purple medulla of the kidney was obsered in one low level male, two intermediate level males, and one high level male. The mucosa of the bladder was reddened in one intermediate level female. A moderate amount of yellowish green mucoid fluid in the stomach and dark green bile in the gallbladder were noted for high level male Dog No. 15459. The cut surface of the kidney was purple in one control female.

#### Organ Weights

Individual organ weights, terminal body weights, and organ/body weight ratios are presented in Table No. 5.

A high adrenal/body weight ratio was noted for low level male Dog No. 15454, a high testes/body weight ratio was observed for intermediate level Dog No. 15448, and a high spleen/body weight ratio was observed for high level male Dog No. 15377 and female Dog No. 15435.

## Microscopic Pathology

The daily intravenous injection of WR 149,024 AD (AX 67287) for 14 consecutive days to male and female beagle dogs produced a relative increase in the parafollicular tissue in the thyroids of females injected at the dosage rates of 10.0 and 20.0 mg/kg of body weight. The size of the thyroid follicles and the morphological characteristics of the follicular epithelium were not meaningfully different from the controls. In the female dogs receiving 20.0 mg/kg of body weight, the increase in parafollicular tissue was more striking than that seen in the females injected with 10.0 mg/kg. A focal hyperplasia of parafollicular tissue was seen in female Dogs No. 15471 and No. 15470 injected with 20.0 and 10.0 mg/kg of body weight, respectively. Careful grading of the amount of parafollicular tissue in the male dogs injected intravenously with WR 149,024 AD (AX 67287) did not reveal any meaningful differences from the control male dogs.

An equivocally greater amount of parafollicular tissue was present in the males injected with 20.0 mg/kg of WR 149,024 AD (AX 67287), but because of the extreme variation in the controls, it was not considered to be related to the injection of the test material. It should also be noted that the amount of parafollicular tissue seen in the female dogs injected with 10.0 and 20.0 mg/kg of body weight was sometimes no greater than that seen in the control and test

males. The increase in thyroid parafollicular tissue observed in the female dogs injected with 10.0 and 20.0 mg/kg of body weight was not consistent and presented a somewhat confusing pattern when these animals were compared in detail with the control females. One female control (Dog No. 15432) had essentially the same amount of parafollicular tissue as that seen in female Dogs No. 15430 and No. 15434 that were injected with 10.0 mg/kg of body weight of WR 149,024 AD (AX 67287). This observation confuses the interpretation of the thyroid findings even further. However, it was felt that the increase in parafollicular tissue was great enough to attribute this finding to the injection of WR 149,024 AD (AX 67287).

Incidental microscopic alterations were seen in the spleen, liver, and kidneys from both the control and test dogs. In the spleen, a minimal to slight amount of pigment deposition was present in both the males and females. The incidence of this pigment deposition was slightly greater in the females, but the test females were not meaningfully different from the controls. Lesions of an incidental nature seen in both the test and control dogs consisted of minimal to slight bile duct proliferation, and the presence of a few bile plugs in some animals.

Minimal mineral deposition was seen in the medulla of the kidneys from the majority of the animals in both the control and test groups. Scattered incidences of chronic lymphocytic interstitial nerphritis were seen in some of the males.

Moderate to severe focal chronic epididymitis was present in one control male Dog No. 15451. This microscopic alteration was characterized by a focal accumulation of spermatozoa surrounded by granulomatous inflammation.

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In conclusion, it can be stated that the intravenous injection of WR 149,024 AD (AX 67287) at the rate of 10.0 and 20.0 mg/kg of body weight per day for a period of 14 days to female beagle dogs resulted in the production of an increase in the amount of parafollicular tissue in the thyroid gland. No other compound-related histopathological alterations were noted in any of the tissues examined from these animals. Microscopic examination of the livers and kidneys from male and female beagle dogs receiving 5.0 and 10.0 mg/kg of body weight per day for a period of 14 days did not reveal any compound-related microscopic alterations.

Submitted by

FREDERICK E. RENO, Ph.D Project Manager, Drugs and Industrial Chemicals Department Toxicology-Biosciences Laboratory

Pathology by

JOHN F. FERRELL, D.V.M. Consultant Pathologist

Report Preparation: Horwatt

Supervision: Upman

dc;gbb

NOTE: The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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# EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

- T = trace (±)
- 0 = negative
- 1 = slight (+)
- 2 = moderate (++)
- 3 = marked (+++)
- 4 = severe (++++)

Table No. 1 - Body weights of beagles receiving WR 149,024 AD (AX 67287)

	,		GROUP NO. 1 .	GROUP NO. 1 - SALINE CONTROL		
TIME INTERVAL	DOG NO. 15358 M	DOG NO. 15398 M	DOG NO. 15451 H	DOG NO. 15319 P	DOG NO. 15432 F	DOG NO. 15436 F
veeks	ľ		kg.	kg.	kg.	kg.
Initial	14.4	10.4	11.3	12.7	10.5	10.1
1	15.0	10.5	11.5	12.5	10.6	10.0
7	14.9	10.7	11.5	12.8	10.5	10.1
Net Change, kg.	,e, +0.5	+0.3	+0.2	+0.1	0	0

Table No. 1 - Continued

	0.000	GKOU	P NO. 2 - 5 MG/KG	OF BODY WEIGHT I	EVEL	
TIME INTERVAL	LUG NO. 15359 M D	DOG NO. 15426 M	DOG NO. 15424 M	DOG NO. 15426 M DOG NO. 15424 M DOG NO. 15322 F DOG 1	15322 F DOG NO. 15433 F DOG NO. 15437 F	DOG NO. 15437 F
veeks	kg.		WEIGHT kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT kg.
Initial	8.8	12.7	13.2	7.0	11.0	6.6
1	0.6	12.0	12.5	9.9	11.4	6.8
7	8.8	12.1	12.5	8.9	11.3	9.5
Net Change, kg.	0	9.0-	-0.7	-0.2	+0*3	-

Table No. 1 - Continued

TIME	•		DOG NO. 15448 M DOG NO. 15458 M DOC NO. 15530 P DOC NO.	DOC NO 15430 P	DOC NO 15/2/ P	
INTERVAL	WEIGHT		WEIGHT	WEIGHT	WEIGHT	WEIGHT LIPS NO. 15470 F
Veeks		kg.	kg.	kg.	kg.	kg.
Initial	10.7	8.0	11.5	8.5	10.4	8.4
	10.0	7.9	10.8	7.7	8.6	8.0
7	11.0	7.7	11.1	7.8	6.6	8.1
Net Change, kg.	e, +0.3	-0.3	-0.4	-0.7	-0.5	-0.3

Table No. 1 - Continued

TIME	(	DOG NO. 154	P NO. 4 - 20 MG/K	GROUP NO. 4 - 20 MG/KG OF BODY WEIGHT LEVEL	LEVEL	
INTERVAL	3	WEIGHT	WEIGHT	DOG NO. 15431 F	DOG NO. 15435 F	8
	•60 **	kg.	kg.	kg.	kg.	WEIGHT
Initial	12.1	8.3	8.5	8.0	6.4	; ° ° °
-	12.0	7.6	7.8	7.8	. v	, o
7	11.8	8.3	8.0	7.3	6.2	0 0 0 r
Net Change. kg.	٠٠ ا	o	-0.5	-0.7	-0.2	-0.7

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES PUREBRED BEAGLES RECEIVING WK149,024 AD (AX67287) FOR TWO WEEKS INITIAL

AN I MAL NUMBER	иш×	HCT *	HGB	RBC	WBC THS	META	BAND	DIFFE SEG %	AND SEG LYMPH	MUND	EDS IN	BASU
	Σ.	2.0	18.7	5.04	8.8	0	0	47	38	4	11	٥
	Z.	53.0	18.7	6.92	8.8	0	-	14	43	· m	9	ن د
15451	Z 7	<b>7.</b> 0	17.2	5.32	19.4	0	0	78	18	M	-	0
GROUP MEAN	Ñ	50.7	18.2	5.96	12.3							
	E C	1.0	18.2	6.28	11.1	0	-	63	28	4	^	c
15426	<u>S</u>	51.5	18.7	7.03	5.6	0	0	55	34	) IN	1 4	) C
15454 N	Z.	1.0	18.2	6.31	11.2	O	၁	62	53	4	· v	ာဝ
GROUP MEAN	Ŋ	51.2	18.4	6.54	9.3							
15360 4	Z.	3.0	18.9	5.91	10.5	0	၁	59	37	0	4	C
	M 57	52.0	18.7	6.28	16.4	0	· つ	78	18	4	· c	o C
15458	Z.	0.5	17.9	5.87	6.5	ပ	၁	53	30	'n	12	0
MEAN	3	51.8	18.5	6.02	11.1							
15377 N	M 56	0.5	18,9	6.34	11.0	0	o	58	S. S.	4	រេ	c
		57.0	19.5	7.26	9.1	0	-	74	23	٠	١ ٥	9 3
5459 4	ر ا	0.0	17.7	0.48	7.6	0	0	10	26	12	7	0
GROUP MEAN	Ŋ	55.5	18.7	69.9	9.2							

TABLE NO. 2 - INDIVIDUAL HEMATULUGICAL VALUES
PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS

		S							UIFFE	DIFFERENTIAL			1 1 1
GROUP	AN IMAL NUMBER	אני	HCT **	HGB GMR	RBC MILLS	WBC	ME TA	BAND &	SEG &	Lymph %	MONU	EUS IN	BASO
	15358	X	52.0	18.7	6.72	8.2	0	0	51	46	-	Ŋ	o
~-	15398	Σ	53.0	18.9	6.51	9.4	0	0	09	35	၁	2	0
-	15451	τ	50.0	17.7	6.18	9.5	0	0	72	26	0	7	0
GROUP !	MEAN		51.7	18.4	24.47	0.6							
2	15359	Z	50.0	17.9		12.9	၁	0	80	19	0		0
۲1	15426	Σ	53.5	18.7	6.64	5.5	0	O	57	42	၁		0
7	15454	Σ	51.0	18.4		7.6	0	0	69	28	٥	m	0
GROUP	MEAN		51.5	18.3	94.9	8.7							
ю	15360	Æ	51.0	17.71	6.17	<b>α</b>	o	0	56	77	၁	0	ပ
m	15448	Σ	55.0	18.7	29.9	6.2	0	0	12	27	ဝ	-	0
m	15458	Σ	5 <b>1.</b> 0	18.6	6.18	0.0	Ö	ဂ	19	32	ဂ	1	0
GROUP MEAN	HEAN		52•3	18.3	6.34	7.0							
4	15377	τ	68°	17.2	5.82	9.1	0	၁	19	38	၁	-	0
4	15449	Σ	58.0	19.9	6.45	5.5	0	၁	73	25	7	၁	0
4	15459	Σ	52.0	18.2	5.95	3.5	ပ	ာ	62	38	၁	0	0
GROUP	MEAN		52.7	13.4	10.9	0.9							

TABLE NO. 2 - INDIVIDUAL HEMATULOGICAL VALUES PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS WEEK 2

						ii Z	MEER 2							
GROUP	ANIMAL NUMBER	SmX	HCT	HGB GM#	RBC MILLS	WBC	META	BAND	DIFFEF SeG	BAND SEG LYMPH MON	MONO	EOS IN	BASU	
	15358 15398 15451	EXX	50.0 52.0 49.5	17.9 18.2 17.7	6.83 7.22 6.72	8.2 10.3 11.4	000	-00	56 56 55	38 37 31	-0-	41-8	000	
GROUP	MEAN		50.5	17.9	6.92	10.0								
222	15359 15426 15454	III	48.0 48.0 51.0	16.7 16.7 17.7	6.60 6.76 6.60	10.3 5.2 7.8	000	000	61 45 57	35 41 38	450	0 4 6	000	
GROUP	MEAN		0.64	17.0	6.65	7.8								
M M M	15360 15448 15458	EEE	46.5 53.0 49.0	15.9 18.2 17.2	6.28 7.28 6.58	13.3 7.2 5.5	000	၀ပ၁	83 60 61	12 39 21	N 0 N	0 1 13	000	
GROUP	MEAN		46.5	17.1	6.71	8.7								
444	15377 15449 15459	EEE	49.0 57.0 46.0	17.2 19.7 15.9	6.25 7.65 6.14	9.5 6.2 3.8	000	00~	54 74 67	45 30	707	<b>%</b> 00	000	
GRUUP MEAN	HEAN		50.7	17.6	6.68	6.5								

TABLE NO. 2 - INDIVIDUAL HEMATULUGICAL VALUES
PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS

S	1	ASU	<b>34</b>	c	, 0	0		0	0	0		Ö	) (3	0		o	· c	0	
<u>.</u>	į																		
] E	!	EUS IN	34	o	ر ا	_		7	, <b>2</b> 0	Ŋ		7	. 4	7		σ	. 4	٠ ~	
5	į								•					•					
MITTACE TO LEAST TO LOS IND MEENS		MONIT	<b>~Q</b>	4	7	7		4	•	C		~	-	~		4	^	<b>.</b>	
7	AF-	ĭ																	
Ì	DIFFERENT IAL	LYMF	34	33	33	<b>4</b> C		45	34	41		29	25	35		24	43	28	
2	FER	ون	<b>~</b>	9	59	19		61	52	٠ <u>٠</u>		7	3	61		Q	=	69	
	110-	ŝ	?*	v	111	311		(4)	ų,	•		L.	0	•		•	.20	9	
	1	MAND	<b>*</b> •	C	_	0		0	9	J		0	0	0		7	0	0	
	- 1																		
TIA		META	<b>34</b>	0	0	0		0	9	0		0	0	O		၁	ပ	•	
INITIAL		ЯC	THS	<b>9</b>		8.2	3.6	ε,	<b>E</b>	8.4	10.C	.2	~	11.7	5	~	6	-	ç
<del>:</del>		3	_	5	10	σ	3r	01	1	80	07	12	1	11	10.5	10	00	15.1	11.6
		RBC	577	96.	6.06	• 32	5.94	. 52	.42	• 20	6.05	.01	44.	<b>9∙</b> €	5,55	.27	00.	6.34	6.20
)		~	X	S	·Đ	ις)	5	S	•9	9	9	σ.	S	3	2	9	9	•	9
		HJB	G 74	6.7	16.5	6.5	16.6	6.5	6.5	16.9	16.6	7.7	6.5	15.9	16.7	7.2	7.2	18.2	17.5
•		HCT	*	46.0	47.0	46.5	46.5	47.0	46.0	47.0	46.7	48.3	46.0	45.0	46.3	48.0	47.0	51.0	48.7
	S	ш	×	4	u_	u_		u_		u.		u.	u.	u_		u.	u.	u_	
		AL	ER	61	32	36		22	33	37		30	34	7.0		31	35	7.1	
		ANIMAL	NUMBER	15319	15432	15436	MEAN	15322	15433	15437	MEAN	15430	15434	15470	MEAN	154	154	15471	A
																			<u>π</u>
		GROUP	NUMBER	-	-		GROUP	7	N	7	GRUUP	3	~	m	GROUP	*	4	4	GROUP MEAN
		e,	Z				G.				S.				3				ر. د

The secretary and participations

			D.	TA Purebreu	BLE NU. BEAGLES	2 - RECEI	2 - INDIVIDUAL HEMA) RECEIVING WR149,024 / WEEK 1	IDUAL	HEMAT. 024 A.	HEMATOLOGICAL VALUES 024 AD (AX67287) FUR	L VALU 287) FI	ES UR TWO	WEEKS
GRUUP NUMBER	ANIMAL NUMBER	νm×	HCT	H GB	RBC MILLS	WBC THS	ME TA	BAND	DIFFEI SEG	-DIFFERENTIAL- SEG LYMPH	MUNU	EUS IN	B ASO
	15319 15432 15436	444	44 43.0 42.0	15.9 15.9 15.2	5.38 5.01 4.96	8.2 9.6 7.1	ပဝခ	000	62 61 65	3 R 88	040	969	000
<u>a</u>	HEAN		43.0	15.7	5.12	8.3							
777	15322 15433 15437	<b></b>	44.0 47.0 39.0	15.9 16.9 14.6	5.47 5.89 5.10	9.3 11.0 9.4	000	000	5 V S	40 41 35	000	7 <b>7</b> 7	000
GROUP	MEAN		43•3	15.8	5.49	6.6							
ммм	15430 15434 15470	<b>u_ u_</b> u_	47.0 50.0 43.0	16.5 17.7 15.4	5.38 5.97 5.30	9.9 6.0 7.4	000	000	69 65 57	28 42 42	-00	7 7 7	000
GROUP	MEAN		46.7	16.5	5.55	7. d							
444	15431 15435 15471	டிடிட	43.0 48.0 48.0	15.4 17.2 17.4	4.76 5.99 5.77	7.9 5.7 5.0	၁၁၁	၁၁၀	9 4 9 9	3 3 3 5 5	ဝဂပ	w00	000
GROUP MEAN	MEAN		46.3	16.7	5.51	6.2							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FUR TWO WEEKS
WEEK 2

10				
BASO	0 0 M	0 10	000	00
EOSIN	14	155	4 9 4	ດ <b>ຕາຕ</b>
MONO	500	722	# C #	8 =
META BAND SEG LYMPH MONO  * * * * * *	32 29 30	4 3 4 3 6 3	23 48 48	27
OIFFEI SEG	61 68 51	51 44 41	70 56 37	67 58
BAND	000	000	000	00
META	000	000	000	00
WBC	8.3 9.5 7.6	8.5 8.4 10.9	9.7 15.0 6.5 8.1	9.9 11.0 8.9 5.6 8.5
RBC MILLS	5.83 5.47 5.71	5.67 6.41 6.19 5.41	6.02 6.18 6.44 5.46	5.53 6.06 5.70 5.70
HGB	15.2 14.6 14.8	16.9 16.3 16.3	15.3 16.3 17.7 14.6	16.2 15.9 16.7 15.9
ĦĊŢ	41.0 41.0 42.0	41.3 49.0 46.0 40.0	45.0 46.0 50.0 42.0	46.0 40.0 49.0 45.0
νшх	<b></b>	444	<b>u. u. u.</b>	<b></b>
AN IMAL NUMBER	15319 15432 15436	MEAN 15322 15433 15437	MEAN 15430 15434 15476	HEAN 15431 15435 15471 MEAN
G ROU P NUMBER		GROUP 2 2 2 2	GRUUP 3 3	GROUP 4 4 4 GROUP

TABLE NO. 2 - INDIVIDUAL HEMATULOGICAL VALUES
PUREBRED BEAGLES RECEIVING WRI49,024 AD (AX67287) FOR TWO WEEKS
INITIAL

ATION	11 35 28	45	111 46 50	56	40 31 58	43	10 07 40	5.6
COAGULATION MIN SEC	440	4	2044	4	n 4 w	4	w w 4	4
SШX	III		ΣΣΣ		ΣΣΣ		IEI	
ANIMAL NUMBER	15358 15398 15451	MEAN	15359 15426 15454	MEAN	15360 15448 15458	MEAN	. 15377 15449 15459	MEAN
GROUP NUMBER		GROUP	888	GROUP	തതത	GKDUP	444	GRUUP

VALUES 7) FOR THO WEEKS PUR

ÍDUAL HEMATULOGICAL V WR149,024 AU (AX67287	COAGULATION Min Sec	35 52 31	65	47 10 58	58	34 38 02	60	004 000	39
> ~	COAGU	w w 4	m	m 4 m	m	4 11 4	4	404	3
N. S.	$\times$ m $\times$	ΣΙΙ		III		ΣΣΣ		III	
2 - RECEI WEE	AN I MAL NUMBER	15358 15398 15451	MEAN	15359 15426 15454	MEAN	15360 15448 15458	MEAN	15377 15449 15459	MEAN
TABLE NU. Rebreij beagles	GROUP NUMBER		GROUP	222	GROUP	๓๓๓	GROUP	444	GRUUP

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
WEEK 2

			٠					
ATION SEC	111 35 28	45	11 46 50	99	40 31 58	43	10 07 40	65
COAGULATION Min sec	440	4	N44	4	10 4 m	4	เขาน 4	4
νшх	III		III		III		EEE	
ANI MAL NUMBER	15358 15398 15451	MEAN	15359 15426 15454	MEAN	15360 15448 15458	MEAN	15377 15449 15459	MEAN
GROUP NUMBER		GROUP	888	GROUP	m m m	GROUP	444	GROUP MEAN

TABLE NO. 2 - INDIVIDUAL HEMATULUGICAL VALUES
PUREBREJ BEAGLES RECEIVING WR149,024 AU (AX67287) FOR TWO WEEKS
INITIAL

ATION SEC	55 36 38	59	42 21 29	51	52 15 44	2.5	27 42 23	
COAGULATION MIN SEC	4 11 4	4	464	4	4104	.†	444	
νшх	444		444		4.4.4.		444	
ANI MAL	15319 15432 15436	MEAN	15322 15433 15437	MEAN	15430 15434 15470	MEAN	15431 15435 15471	
GROUP		GROUP	202	GROUP	ммм	GRUUP	444	

31

GRUUP MEAN

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
PUREHRED BEAGLES RECEIVING WRI49,024 AD (AX67287) FOR TWU WELKS
WEEK 1

ATION SEC	11	54	45	25	94	55	15	51	28	<del>ر</del> 0	20	20	43	15	99	38
COAGULATION Min Sec	4	m	m	æ	m	e	m	6 <b>9</b>	4	4	4	4	יזי	~	æ	٤
νшх	u,	Ţ	<u>u</u>		ų.	ų,	u.		ш,	щ	ų.		u_	4	u.	
ANI MAL NUMBER	15319	15432	15436	MEAN	15322	15433	15437	MEAN	15430	15434	15470	MEAN	15431			IE AN
GROUP	7	~	~	GROUP !	7	7	7	GROUP	3	m	'n	GROUP "	4	4	4	GROUP MEAN

•

K TWO WEEKS PUR

TA Rebred	TABLE NO. D BEAGLES	2 - RECEI WEE	102 103 103 103 103 103 103 103 103 103 103		VIDUAL HEMATOLOGICAL VAL WR149,024 AD (AX67287) 2	VALUES 7) FOR
	GROUP	ANI MAL NUMBER	SШX	COAGULATION Min Sec	ATION Sec	
		15319 15432 15436	444	<b>ተጠ</b> ታ	15 56 38	
	GROUP	HEAN		4	16	
	000	15322 15433 15437	<b></b>	<b>ት</b> ለ ቀ	42 21 29	
	GROUP	MEAN		4	51	
	m m m	15430 15434 15470	444	4114	52 15 44	
	GROUP	MEAN		4	15	
	444	15431 15435 15471		444	27 42 43	
	GROUP	MEAN		4	37	

TWO WEEKS - INDIVIDUAL BLOOD CHEMISTRY VALUES TABLE NO. 3

		٠,					BILIRUBIN	
GUCINE	ANIMAL	ш	GLUCUSE	BUN	SGPT	ALK. PHOS	TOTAL	2001
NUMBER		×	99W	MG &	スード・	K-A. UNITS	MC&	K. UNITS
٠	4 2 5 2	2	0.58	14.3	27.0	5.1	0.35	0.44
	2004		0.40	14.0	25.0	2.6	0,33	41.0
	15451		0.4.0	12.0	19.0	0 • 9	0.21	33.0
GROUP	MEAN		83.3	13.3	23.7	4.6	0.30	39•3
•	16369	3	76.0	16.0	24.0	5.8	0.29	37.0
۰ د	15676		87.0	8.0	32.0	4.5	0.29	25.0
7	15454		88.0	10.5	24.0	13.0	0.29	33.0
GRUUP	MEAN		83.7	11.5	26.7	7.8	0.29	31.7
.4	15360	Σ	70.0	14.0	22.0	8.5	0.30	39.0
4 ،	15448	I	85.0	۵.	29.0	4.5	0.29	43.0
~	15458		99.0	11.0	38.0	8.0	0.30	45.0
GROUP	MEAN		84.7	11.0	29.7	7.0	0.30	41.3
4	15377	3	62.0	22.0	22.0	4.9	0.30	39.0
. 4	15449		93.0	14.0	22.0	၁•6	0.31	37.0
. 4	15459	Σ	95.0	11.0	32.0	0 • 6	0.30	45.0
GROUP	MEAN		8.5.3	15.7	25.3	7.6	0.30	39.3

TWO WEEKS

GROUP NUMBER	AN IMAL	νшх	GLUCUSE MG%	BUN	SGPT R-F.	ALK. PHUS K-A. UNITS	BILIRUBIN TOTAL MG\$	SGUT K. UNITS
-	15358	Σ	96.0	11.0	38.0	9.6	0. 31	67
	15348		0.06	16.0	35.0	0	10.0	
	15451	ŧ	92.0	11.0	32.0	70	6.21	44.0
GROUP	MEAN		92.1	12.7	35.0	7.1	0.23	43.0
2	15359		85.0	24.0	28.0	8 9	0.20	0.64
7	15426		96.0	11.0	35.0	6.1	0.26	27.0
7	15454	Σ	96.0	8.5	32.6	10.2	0.21	41.0
GROUP	MEAN		92.3	14.5	31.7	7.7	0 - 22	40.0
٣	15360	¥	86.0	19.0	31.0	8-6	0,20	47
m	15448	Σ		11.0	39.0	0 9	07.0	0 0 0
m	15458	Σ	115.0	15.0	38.0	10.0	0.19	45.0
GRUUP .	HEAN		108.3	15.0	36.€	8.6	0• 20	44.7
4	15377	Σ	0.56	18.0	41.0	6•9	0.30	6.8
4	15449	Σ		15.0	31.0	10.0	0.00	0 0 0
4	15459	Ŧ.		15.0	29.0	0.6	0.20	0.44
GRUUP MEAN	N F A N			•				

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS WEEK 2

	GROUP AN I NUMBER NUM	1 15		61 1	GROUP MEAN	2 15		~	GROUP MEAN	3 15		3 154	GROUP MEAN	4 153	4 154	4 154		GROUP MEAN
	S ANIMAL E NUMBER X	5358 M		H 1046		5359 H	5426 M	5454 M		15360 M	448 M	5458 R		15377 M	X 641	15459 M	:	
	GLUCUSE MG#	94.0	0.66	91.0	7.46	96.0	100.0	90.0	95.3	85.0	111.0	105.0	100.3	92.0	114.0	106.0	) • ) • )	104.0
	BCN	11.0	12.0	9.	10.8	21.0	12.0	0.6	14.0	41.0	10.0	14.0	21.7	18.0	15.0	12.0	76.0	15.0
	SGPT R-F.	36.0	35.0	32.0	34.3	32.0	38.0	35.0	35.0	32.0	36.0	39.0	35.7	39.0	29.0	,	26.0	33.3
7 WILL 7	ALK. PHUS K-A. UNITS	7.2	5.9	0 • 9	<b>6.</b> 4	6.2	6.2	8.6	7.0	8.6	6.9	8.2	8•3	5.8		) ( ) )	6•9	7.2
	BILIRUBIN Total MG%	0•36	0.29	0. 29	0.31	0.25	0.30	0.25	0.27	0-22	0.22	0.20	0.21	0.20		67.0	0* 50	0.26
	SGOT K. UNITS	37.0	35.0	27.0	33.0	36	0 0	30.0	32.3	9	20°14	33.0	34.0	, ,	75.0	31.0	33.0	35,3

- INDIVIDUAL BLOUD CHEMISTRY VALUES TABLE NU. 3

	AN I MAL NUNBER	SШ×	GLUCOSE MG%	NOW NOW	SCPT R-F.	ALK. PHUS K-A. UNITS	BILIRUBIN TOTAL MG%	SGUT K.UNITS
	15319	u.	82.0	14.5	31.0	2.8	0.29	43.0
-	15432		71.0	11.0	29.0	6.0	0.30	0.64
	15436	u.	0.66	17.0	25.0	2.8	0.29	6.04
GROUP ME	MEAN		84.0	14.2	28.3	3.9	0.29	0.44
7		u_	70.0	14.5	24.0	4.0	0.29	40.0
7	15433	u.	93.0	15.5	27.0	2.8	0.30	38.0
7	15437	<u>u</u>	82.0	14.0	25.0	4.0	0.29	43.0
CROUP ME	MEAN		81.7	14.7	25.3	3.6	0.29	40.3
	15430	ı.	ე•ņ6	10.0	28.0	11.1	0.29	0.64
πì		u	95.0	0.7	25.0	4.4	<b>0.30</b>	43.0
	15410	u	76.0	18.0	25.0	3.3	0.21	41.0
GROUP ME	MEAN		87.0	11.7	26.0	6.3	0.27	46.3
4	15431	u.	74.0	13.0	29.0	12.2	0.22	46.0
4	15435	Ľ.	88.0	13.0	24.0	3.1	0.20	45.0
4	15471	ů.	82.0	12.0	27.0	8.2	0.49	43.0
GROUP MEAN	AN		81.3	12.7	26.7	7.8	6.30	43.7

O WEEKS

GROUP	ANIMAL R NIMBER	×пν	GLUCU SE MG 2	NON	SGPT	ALK. PHOS	BILIRUBIN TOTAL	1098
			• 5 5	<b>*</b>	L	K-A. UNIIS	M C M	K.UNITS
-	15319		92.0	11.5	28.0	5.0	0. 21	•
~	15432		84.0	16.3	35.0	0.0	0.21	) () () ()
-	15436	ų.	101.0	18.0	31.0	5.0	0.21	43.0
GROUP	MEAN		92.3	15.2	31.3	<b>6.</b> 4	0.21	0.44
7	15322	u.	85.0	17.0	28.0	ŭ		6
~	15433		105.0	17.0	31.0	, r.	17.0	
7	15437	ı.	105.0	12.0	29.0	7.8	0.30	42.0
GROUP MEAN	MEAN		98.7	15.3	29.3	6.5	3.24	44.3
m	15430	u.	165.0	11.9	29.0	-	o o	
m	15434	u.		12.0	0 0	7	0.50	) • · · ·
m	15470	u.		21.0	32.0	7.5	0.20	44°C 52°O
GRÜUP	MEAN		103.3	14.7	33.0	8.2	0. 20	47.3
4	15431	u_	102.0	14.0	32.0	14.9	0.19	2
4	15435	u.		14.0	28.0	7.0	000	0 0
4	15471	u.	0.001	13.0	27.0	7.2	0° 30	47.0
GKOUP	MEAN		108.7	13, 7	29.0	<b>7.</b> 6	0. 23	48.7

			Z Z	FUNEBRED DEAGLES RELEIVING WRITY;024 AD 1AA612811 FUR INU Week 2	! !	WEEK 2				
GROUP		N m	GLUCUSE	BUN	SGPT	ALK. PHUS	BIL IRUBIN TOTAL	SG0T		
NUMBER	R NUMBER		₩6 <i>¥</i>	₩C.₩	R-F.	K-A. UNITS	MGK	K.UNITS		
-	15319		95.0	13.0	29.0	5.2	0.29	31.0		
-	15432	u_	85.0	15.0	36.0	8.9	0.30	39.0		
-	15436		102.0	15.5	34.0	5.2	0.22	33.0		
GROUP	MEAN		93.0	14.5	33.0	<b>6.</b> 4	0.27	34.3		
7	15322		89.0	24.5	35.0	5.4	0.21	37.0		
7	15433	u_	106.0	15.0	28.0	5.C	0.21	33.0		
~	15437		100.0	13.0	29.0	6.9	0.25	29.0		
GROUP	MEAN		98.3	17.5	30.7	5.8	0.22	33.0		
m	15430		91.0	17.0	28.0	10.0	0.20	33.0		
æ	15434	u.	106.0	13.0	35.0	5.9	0,30	36.0		
m	15470		105.0	18.0	31.0	7.1	0.24	40.0		
GROUP	MEAN		100.7	16.0	31.3	1.1	0.25	36.3		
•	15431		110.0	13.0	32.0	12.1	0.20	39.0		
*	15435	u.	36.0	15.5	28.0	7.6	0.21	37.0		
4	15471		109.0	12.0	28.0	0.9	0.30	31.0		
GROUP MEAN	MEAN		101.7	13.5	29.3	8.6	0.24	35.7		

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TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES PUREBRED BEAGLES RECEIVING WRI49,024 AD (AX47287) FUR TWD WEEKS

GROUP NUMBER	ANIMAL	×πν	SEKUM SODIUM MEQ/L	SERUM PUTASSIUM MEQ/L	SERUM LLORIDE MEQ/L	SERUM CALCIUM AG&	C02 MEQ/L
-	15358	Σ	145.0	4.45	112.0	10.6	25.8
_	15398	Σ	145.0	4.55	112.0	10.6	25.2
~	15451		145.0	4.75	108.5	10.5	26.1
GROUP	MEAN		145.0	4.58	110.8	10.6	25.7
~	15359	Σ	146.0	4.50	112.0	10,5	26.1
~	15426	Σ	145.0	5.45	110.0	10.7	28.0
~	15454	Σ	144.0	2.00	106.0	11.0	26.1
GROUP	MEAN		145.0	4.95	109.3	10.7	26.7
m	15360	Σ	146.0	4.10	112.0	10.6	25.2
ď	15448	I	147.0	5.70	110.0	10.8	26.9
~	15458	Σ	144.0	5.30	110.0	10.3	26.8
GROUP	MEAN		145.7	5.03	110.7	10.6	26.3
4	15377	I	148.0	04.4	113.0	11.3	26.0
4	15449		144.0	00.9	105.0	11.3	27.6
.,	15459	Æ	143.0	5.10	107.0	10.1	26.5
:	;		,	•			,

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES PUREBRED BEAGLES KECEIVING WRI49,024 AD (AX67287) FOR TWO WEEKS

91000	4 M T 18 A	S	SERUM	SERUM	SERUM	SERUM	( !
NUMBER	NUMBER	u ×	MEQ/L	MED/L	CHLUKIUE MEU/L	CALCIUM MG%	CCC MEQ/L
-	15358	×	148.0	4.95	103.5	11.2	25.3
-	15398		148.0	4.50	114.0	10.9	24.2
-	15451		145.0	4.66	112.0	10.6	24.5
GROUP	MEAN		147.0	4.68	109.8	10.9	24.7
2	15359	Σ	140.0	4.10	114.0	10.5	24.9
7	15426	X.	144.0	2.00	113.0	10.6	25.0
7	15454	Σ	145.0	5.05	113.5	10.5	24.9
GROUP ,	MEAN		145.0	4.72	113.5	10.5	24.9
	15360	X.	147.0	4.30	113.0	10.2	25.1
m	15448	Z.	147.0	5.10	113.0	10.6	23.8
m	15458		147.0	4.80	114.0	10.3	23.9
GROUP	MEAN		147.0	4.73	113,3	10.4	24.3
4	15377	Σ	148.0	3.80	114.0	10.8	24.5
4	15449	Σ	148.0	4.90	111.0	11.2	25.0
4	15459		148.0	4.50	114.6	10.5	26.6
GRINID	N C U		0 0 7 1		,		

WEEKS

		S	SERUM	SERUM	SERUM	SERUM	
GROUP	ANIMAL	w	SODICA	POTASSI UM	CHLOR 1 DE	CALCIUM	C 02
NUMBER	NUMBER	×	MEQ/L	MEQ/L	MEQ/L	#9#	MEQ/L
-	15358	Σ	146.0	4.80	112.0	11.0	26.1
_	15398	I	146.0	2.00	111.0	10.8	26.2
-1	15451	I	146.0	4.45	1111.0	10.6	25.2
GROUP	MEAN		146.0	4.75	1111.3	10.8	25.8
2	15359	X	145.0	4.40	112.0	10.6	24.9
7	15426	I	147.0	<b>6.9</b> 0	112.0	10.8	25.8
7	15454	I	147.0	<b>2°</b> 00	114.0	10.8	24.8
GROUP	MEAN		146.3	4.77	112.7	10.7	25.2
М	15360	Z	150.0	4.10	117.0	10.9	24.1
m	15448	E	145.0	5.30	111.0	10.6	24.1
m	15458	Σ	146.0	<b>4.</b> 80	114.0	10.4	23.8
GROUP	MEAN		147.0	4.73	114.0	10.6	24.0
4	15377	Σ	149.0	4.20	115.0	11.1	24.9
<b>4</b>	15449	Σ	148.0	5.00	111.0	11.5	26.0
4	15459	I	148.0	04.4	115.0	10.1	27.0
GROUP	# EAN		148.3	4.53	113.7	10.9	26.0

- INDIVIDUAL BLOOD CHEMISTRY VALUES TABLE NO. 3

a no an	100	S u	SERUM	SEKUN	SERUM	SERUM	503
NUMBER	NUMBER	×	MEQ/L	MEQ/L	MEQ/L	MGK	MEQ/L
~		u.	143.0	4.80	109.0	10.5	24.6
		u_	143.0	4.60	109.0	10.8	24.9
-		u.	146.0	5.30	110.0	11.2	23.0
GROUP	MEAN		144.0	06.4	109.3	10.8	24.2
?		u.	144.0	4.60	109.0	10.5	26.1
7		ī	143.0	4. BC	108.0	11.0	26.0
7	15437	u_	146.0	5.05	108.0	10.8	25.7
GKUUP	MEAN		144.3	4.82	108.3	10.8	25.9
۴	15430	u.	145.0	4.30	108.0	10.7	28.4
4	15434	L	147.0	2.00	109.0	11.0	25.0
~	15470	u.	146.0	2.60	111.0	10.2	26.5
GRUUP	MEAN		146.0	4.97	109.3	10.6	26.6
4			145.0	5.50	111.0	10.4	26.0
4	15435	i.e.	148.0	5.25	111.0	10.0	25.2
4		u.	146.0	5.10	111.0	10.2	24.8
GROUP MEAN	MEAN		146.3	A. 28	7 7 7	10.2	26.2

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES PUREBRED BEAGLES RECEIVING WR149.024 AD (AX67287) FOR TWO WEEKS WEEK 1

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				MEN K	-4		
GROUP NUMBER	ANIMAL	νш×	SERUM SODIUM MEQ/L	SERUM POTASSIUM MEU/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MGZ	C02 MEU/L
-4		ı.	144.0	06**	111.0	10.6	24.2
	15432	u.	145.0	4.80	112.0	11.0	22.8
7		u_	144.0	4.05	115.0	10.6	21.8
GROUP	MEAN		144.3	4.78	112.7	10.7	22.9
2	15322	u_	148.0	07.4	113.5	10.4	25.8
2	15433	ı	1.7.0	7.90	112.0	10.7	22.8
~	15437	L.	145.0	4.55	110.0	10.6	22.6
GROUP	MEAN		146.7	4.62	111.8	10.6	23.7
*1	15430	4	149.0	4.30	115.0	10.1	25.9
M	15434	u.	148.0	4.30	114.5	10.9	24.0
~		u.	148.0	5.36	113.5	10.6	25.8
GROUP	MEAN		148.3	4.63	114.3	10.5	25.2
4	15431	u.	149.0	3.65	115.0	10.4	25.6
4		ц.	146.0	4.40	114.0	10.3	24.0
4		u <u>.                                    </u>	147.0	4.40	114.0	11.0	24.8
GADUP MEAN	MEAN		147.3	4.15	114.3	10.6	24.8

WEEKS - INDIVIDUAL BLUUD CHEMISTRY VALUES TABLE NO. 3

GROUP NUMBER	ANIMAL	νшх	SERUM SUDIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLURIDE MEQ/L	SERUM CALCIUM MG&	C02 MEQ/L
-	15319		144.0	<b>6.90</b>	111.0	10.1	25.9
	15432	<b></b>	144.0	4 • 80 0 8 • 0	111.5	10.6 10.3	24.5 23.2
GROUP	MEAN		144.0	4.83	112.3	10.5	24.5
22	15322		148.0	4.45	114.0	10.5	28.1
7	15437	u.	144.0	4.60	111.0	10.7	24.0
GRCUP	MEAN		146.0	4.75	112.7	10.7	25.2
m	15430	u.	151.0	4.10	119.0	10.8	24.8
m m	15434	<b></b>	151.0 148.0	4.60 5.05	117.0 115.0	10.8 10.6	23.5 26.1
GROUP	MEAN		150.0	4.58	117.0	10.7	24.8
4	15431		150.0	3.95	116.5	10.2	26.2
4 4	15435	u u	149.0	4.70 4.30	113.0 113.0	10.4	25.1 26.9
GROUP	MEAN		149.3	4.32	114.2	10.4	26.1

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS
INITIAL

		J	TOTAL		9   9   9   9   9   9   9   9   9   9	-FI ECTROPHORESTS-	RFS15		TOTAL
G KOUP NUMBER	AN IMAL NUMBER	ш×	PRUTEIN 6%	AL BUMIN	ALPHA1	ALPHA2	BETA %	GAMMA K	ALBUMIN G\$
	X X X X	7	9.5	60.5	4.0	ער מ	24.0	0.4	3,10
-	15398	Σ.	000	53.0	9	11.0	22.5		2.71
·	15451	Σ	5.99	47.0	5.0	15.0	26.5	6.5	2.60
GROUP	MEAN		96•5	53.5	5.0	11.5	24.0	0.9	2.80
2	15359	X	5.31	54.5	4.5	11.0	24.0	0.9	2.95
2	15426	Æ	5.60	52.0	7.0	11.0	24.0	0.9	2.69
7	15454	Σ	6.49	40.0	5.0	15.0	30.0	10.0	2.70
GROUP I	MEAN		00.9	48°8	5.5	12.3	26.0	7.3	2.78
3	15360	Σ	5.71	59.0	5.0	12.0	21.0	3.0	2.70
ec.	15448	Σ	6.20	53.0	0.9	12.5	23.5	5.0	2.60
en.	15458	<b>X</b>	5.50	50.0	η <b>.</b>	15.0	17.0	4.0	3.40
GROUP MEAN	MEAN		5.30	56.0	6.3	13.2	20.5	4.0	2.90
4	15377	Σ	00.3	52.0	7.0	11.0	23.0	7.0	3.35
4	15449	Σ	o.50	49.C	<b>5</b> • C	11.0	29.0	0.9	3.79
4	15459	æ	5.91	96.0	8•0	13.0	21.0	2.0	2.90
GRUUP MEAN	MEAN		6.14	52.3	6.7	11.7	24.3	5.0	3.35

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES

		'n	TOTAL			-ELECTROPHURESIS-	RESIS	1	TUTAL
GRUUP		æ	PROTEIN	ALBUMIN	41	AL PHA2	DETA	GAMMA	ALBUMIN
NOMBER	NUMBER	×	č.	<b>*†</b>	₩	<b>9€</b>	**	<b>∂</b> ₹	<b>2</b> 5
-	15358	Σ	6.30	52.0	<b>4.</b> C	8.5	26.0	0.6	3.09
<b>,</b> 4	15398	τ	67.9	51.0	4.5	9.5	22.5	12.5	2.90
-	15451	£	5. 31	51.0	3.0	14.0	24.0		2.89
GROUP	MEAN		0.13	51.3	3.8	10.7	24.2	8 • 6	2.96
7	15359	X	6.00	51.0	4•0	0.6	29.0	7.0	2.78
7	15426	E	5.65	51.0	4.5	14.5	21.0	0.5	2.78
7	15454	Σ	5. Bl	0.00	<b>6.</b> 0	14.0	24.0	8.0	2.65
GROUP MEAN	MEAN		5.82	50.7	4.2	12.5	24.7	8•0	2.74
Μ	15360		5.40	49.0	0.9	12.0	25.0	8	5.49
m	15443	Σ	6.10	48°C	4.0	13.0	24.0	11.0	2.90
9	15458		5.60	20°C	O •9	13.0	21.0	5.0	3.40
GRUUP	MEAN		5.70	0.64	5.3	14.3	23.3	8.0	2.93
4	15377	Σ	5.60	51.0	5.0	17.0	20.0	7.3	3.48
4	15449	Z	5.99	50.0	0.9	15.0	24.0	5.0	3.60
4	15459	Σ	5.85	24.0	5 <b>.</b> 0	14.0	23.0	4.0	2.99
GROUP MEAN	MEAN		5.41	51.7	κ	4	5	r u	ć

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FOR TWO WEEKS

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		S TOTAL			FLECTROPHORESIS-	IR FS I S	† † † †	TOTAL
G ROUP NUMBER	AN I MAL NUMBER	E PROTEIN	ALBUMIN	ALPHA1 *	ALPHA2	BETA	GAMMA 2	ALBUMIN G&
-	15358		53.5	<b>7</b>	14.0	22.5	0.9	3.20
	15398	H 5.91	49.0	4.0	11.0	25.5	10.5	2.81
	15451	M 5.61	53.0	4.5	14.5	21.0	7.0	3.00
GROUP	MEAN	5.84	51.8	4.2	13.2	23.0	7.8	3.00
7	15359	M 5.90	52.0	4.0	16.0	19.0	0.6	3.05
7	15426	M 5.60	57.0	<b>2°</b> 0	11.5	18.0	8 8	3,19
7	15454	M 5.80	48.0	0.0	16.0	21.0	0.6	2.89
GROUP	MEAN	5.17	52.3	5.0	14.5	19.3	8.8	3.04
m	15360	M 6.20	49.0	5.5	11.5	27.0	7.0	2.80
m	15448	M 5.91	52.0	4.5	10.5	26.5	6.5	2.83
m	15458	M 5.50	55.0	<b>6.</b> 0	13.5	21.5	0.9	3.49
GROUP !	MEAN	5.87	52.0	4.7	11.8	25.0	6.5	3.04
4	15377	M 6.11	56.0	3.0	0.6	23.0	0 <b>°</b> 6	3.49
4	15449	M 6.29	54.0	5.0	11.0	25.0	5.0	3.80
4	15459	M 5.50	29.0	3.0	11.0	20.0	7.0	3.00
GROUP MEAN	1EAN	5.97	56.3	3.7	10.3	22.7	7.0	3.43

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES PUREBRED BEAGLES RECEIVING WR149.024 AD (AX67287) FOR TWO WEEKS

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		S	TOTAL	1		TELECTOOMORY	0.000		4 4 4 6 4
GRUUP NUMBER	AN IMAL	w ×	PROTEIN G&	AL BUMIN	ALPHA1	ALPHA2	BETA	GAMMA	ALBUMIN GK
-	15319	щ	5.71	58.0	7.0	11.6	18.0	0-4	3.40
	15432		6.49	44.0	0 • 9	12.0	\$ . T	2 6	0
	15436		5,65	0.44	7.0	13.0	29.0	7.0	2.66
GROUP MEAN	MEAN		5.95	48.7	1.9	12.0	26.0	6.7	2.96
~	15322		5.70	45.0	7.0	13.0	26.0	0.6	27.74
~	15433	ů.	6.20	46.0	0.9	10.0	31.0	7.0	2.75
ત્ય	15437		00.9	43.0	7.0	13.0	29.0	8.0	3.50
GROUP MEAN	HEAN		5.97	44.7	1.9	12.0	28.7	8.0	3.00
٣	15430	u.	9.30	52°C	6.0	10.5	25.5	0.49	2.40
₹ .	15434		5.99	48.0	<b>6.</b> 0	11.0	27.0	0 0	3.91
M	15470	_	60.4	52.0	<b>0 • 9</b>	12.0	24.0	0.9	2.50
GROUP !	MEAN		5.69	50.7	0.9	11.2	25.5	6.7	3.10
4	15431	1	5.70	53.5	5.5	12.0	22.0	7.0	7
4	15435	u.	4.89	52.0	7.0	12.0	22.0	7.0	
4	15471	u,	2.90	43.0	0 • 9	19.0	26.0	0.0	2.55
GROUP MEAN	MEAN		2°9C	49.5	6.2	14.3	23.3	1.9	2.85

TABLE NU. 3 - INDIVIDUAL BLOUD CHEMISTRY VALUES PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FUR TWO WEEKS WEEK 1

		v	TUTAL	1 1 1 1 1 1 1	# 1	FLECTROPHO	RES I S	1111111	TUTAL
G ROUP NUMBER	AN I MAL NUMBER	m ×	PRUTE IN GX	AL BUM IN	ALPHA1 *	ALPHA2	BETA	GAMMA	ALBUMIN
	15319	<b>L</b>	5.69	50.5	6.5	13.0	22.0	8	3.39
-	15432	<b>LL</b> _	6.41	43°C	0.9	11.0	31.0	0.6	2,71
~	15436		5.59	53∙€	5•0	11.5	22.0	7.0	2.61
GROUP MEAN	HEAN		2.90	43.8	6.3	11.8	25.0	8.0	2.96
2	15322	u.	5.40	52.0	5.0	. 14.5	23.0	5.5	2.80
7	15433		6.10	48.0	6.5	13.C	24.5	ð•0	2.91
7	15437	u.	6.11	49.0	7.0	10.0	27.5	6.5	3,42
GRUUP MEAN	MEAN		5.87	1.64	6.2	12.5	25.0	6.7	3.04
8	15430	<u>u</u>	66.5	47.5	5.5	12.0	25.0	10.0	2.91
Æ	15434		6.30	53.0	0•9	11.0	26.0	4.0	4.00
~	15470		6.21	47.0	8•0	0.0	30.0	0.9	3.29
GROUP MEAN	MEAN		6.17	49.2	6.5	10.7	27.0	1.9	3.40
4	15431	u.	5.90	÷8•0	ი•9	14.0	24.0	8.0	3.50
4	15435		5.30	53.0	ე•9	14.0	21.0	0.9	2,81
4	15471		6.15	48.5	6.5	17.0	23.5	4.5	3.02
GROUP MEAN	MEAN		5.78	46.8	6.2	15.0	22.3	6.2	3,11

PRUTE IN         ALBUMIN         ALPHAI         ALPHAZ         BETA         GAMMA           6x         <			S	TOTAL		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	-FIFCTROPHORECIC	WFC18		TOTAL
319 F       5.70       51.0       6.5       14.5       22.5       5.5         432 F       6.40       45.5       6.0       16.5       23.0       9.0         436 F       5.31       56.0       4.0       12.5       22.0       7.0         1       5.80       50.8       5.5       14.5       22.0       7.2         322 F       5.50       46.0       7.0       15.0       23.0       7.2         433 F       5.91       46.0       7.2       12.8       26.5       6.5         433 F       6.10       46.0       7.2       12.8       26.5       8.0         430 F       6.40       50.0       7.2       12.8       26.5       8.0         434 F       6.41       59.0       3.0       8.5       24.5       5.0         470 F       6.00       57.0       6.0       8.5       22.0       7.8         435 F       5.40       55.3       4.7       9.2       24.5       5.0         435 F       5.40       55.0       5.0       22.0       7.0       5.0         435 F       5.40       55.0       20.5       5.0       5.0       5.0	SROUP NUMBER		m ×	PRUTE IN GK	AL BUM IN	AL PHA 1 %	ALPHA2	BETA	GAMMA	AL BUMIN 6%
1432 F 6.40 45.5 6.0 16.5 23.0 9.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1		15319		5.70	51.0	6.5	14.5	22.5	ري د د	17.61
132 F 5.81 56.0 4.0 12.5 20.5 7.0  1322 F 5.80 50.8 5.5 14.5 22.0 7.2  433 F 5.91 46.0 6.5 12.5 28.5 6.5  433 F 6.10 46.0 7.2 12.8 26.5 8.0  430 F 6.40 50.0 5.0 10.5 26.5 8.0  430 F 6.41 59.0 8.0 10.5 26.5 8.0  431 F 5.95 51.5 6.0 8.5 12.0 22.0 7.0  431 F 5.95 51.5 5.5 12.0 22.0 7.0  435 F 5.40 55.0 5.0 13.5 20.5 6.0  437 F 6.00 54.0 12.5 22.0 5.0		15432		04.9	45.5	0.9	16.5	23.0	0.0	2.84
1322 F 5.80 50.8 5.5 14.5 22.0 7.2 433 F 5.91 46.0 6.5 12.5 28.5 6.5 437 F 6.10 46.0 7.0 15.0 23.0 9.0 437 F 6.40 6.0 11.0 27.0 8.0 430 F 6.40 50.0 5.0 10.5 26.5 8.0 434 F 6.41 59.0 8.0 10.5 24.5 5.0 434 F 6.00 57.0 6.0 8.5 24.5 5.0 431 F 5.95 51.5 5.5 12.0 22.0 7.0 431 F 5.95 51.5 5.0 12.0 22.0 6.0 431 F 5.95 51.5 5.0 12.0 22.0 5.0 471 F 6.00 54.0 7.0 12.0 22.0 5.0	-	15436		5.31	999	<b>4•</b> 0	12.5	20.5	7.0	2.62
433 F       5.50       46.0       6.5       12.5       28.5       6.5         433 F       5.91       46.0       7.0       15.0       23.0       9.0         437 F       6.10       46.0       7.2       12.8       26.5       8.0         430 F       6.40       50.0       5.0       10.5       26.5       7.8         430 F       6.41       59.0       3.0       8.5       24.5       5.0         434 F       6.00       57.0       6.0       8.5       24.5       5.0         431 F       5.95       51.5       5.5       12.0       22.0       7.0         435 F       5.40       55.0       5.0       13.5       20.5       6.0         435 F       5.40       55.0       7.0       5.0       5.0       5.0         471 F       6.00       54.0       7.0       12.0       22.0       5.0         5.78       53.5       5.8       12.5       21.5       6.0	RUUP	MEAN		5.80	50.8	5.5	14.5	22.0	7.2	2.96
433 F       5.91       46.0       7.0       15.0       23.0       9.0         437 F       6.10       46.0       7.2       11.0       27.3       9.0         430 F       6.40       50.0       7.2       12.8       26.5       8.0         430 F       6.41       59.0       3.0       8.5       24.5       5.0         470 F       6.00       57.0       6.0       8.5       24.5       5.0         431 F       5.95       57.0       6.0       8.5       24.5       5.0         435 F       5.40       55.3       4.7       9.2       24.8       6.0         435 F       5.40       55.0       12.0       22.0       7.0         435 F       5.40       55.0       5.5       12.0       5.0         435 F       5.40       55.0       5.5       12.0       5.0         435 F       5.40       55.0       5.0       5.0       5.0         435 F       5.40       55.0       5.0       5.0       5.0         435 F       5.40       55.0       5.0       5.0       5.0         5.78       5.5       12.0       5.0       5.0	7	15322	u,	5.50	46.0	6.5	12.5	28.5	6.5	2.7.1
430 F 6.10 46.0 8.0 11.0 27.0 8.0 430 F 6.40 50.0 5.0 10.5 26.5 8.0 434 F 6.41 59.0 3.0 8.5 24.5 5.0 470 F 6.00 57.0 6.0 8.5 23.5 5.0 435 F 5.40 55.0 5.0 12.0 22.0 7.0 435 F 5.40 55.0 5.0 13.5 20.5 6.0 471 F 6.00 54.0 7.0 12.0 22.0 5.0	7	15433		5.91	46.0	7.0	15.0	23.0	0.6	2.89
430 F       6.40       5.00       10.5       26.5       7.8         430 F       6.40       50.0       5.0       10.5       26.5       8.0         434 F       6.41       59.7       3.0       10.5       24.5       5.0         470 F       6.00       57.0       6.0       8.5       24.5       5.0         471 F       5.95       51.5       5.5       12.0       22.0       7.0         431 F       5.95       51.5       5.5       12.0       22.0       7.0         435 F       5.40       55.0       5.0       13.5       20.5       6.0         471 F       6.00       54.0       7.0       12.0       22.0       5.0         5.78       53.5       5.8       12.5       21.5       6.0	7	15437		<b>6.1</b> 0	46.0	8.0	11.0	27.0	8 • 0	3.49
430 F 6.40 50.0 5.0 10.5 26.5 8.0 434 F 6.41 59.7 3.0 8.5 24.5 5.0 470 F 6.00 57.0 6.0 8.5 23.5 5.0 431 F 5.95 51.5 5.5 12.0 22.0 7.0 435 F 5.40 55.0 7.0 13.5 20.5 6.0 471 F 6.00 54.0 7.0 12.0 22.0 5.0		MEAN		5.84	46.0	7.2	12.8	26.2	7.8	3.03
434 F 6.41 59.7 3.0 8.5 24.5 5.0 470 F 6.00 57.0 6.0 8.5 23.5 5.0 6.27 55.3 4.7 9.2 24.8 6.0 431 F 5.95 51.5 5.5 12.0 22.0 7.0 435 F 5.40 55.0 5.0 13.5 20.5 6.0 471 F 6.00 54.0 7.0 12.0 5.0	6	15430		0.40	50.0	5.0	10.5	26.5	8.0	3.05
470 F 6.00 57.0 6.0 8.5 23.5 5.0 6.27 55.3 4.7 9.2 24.8 6.0 431 F 5.95 51.5 5.5 12.0 22.0 7.0 435 F 5.40 55.0 5.0 13.5 20.5 6.0 471 F 6.00 54.0 7.0 12.0 5.0	m	15434		6.41	59.0	3° C	8.5	24.5	5.0	4.25
6.27       55.3       4.7       9.2       24.8       6.0         431 F       5.95       51.5       5.5       12.0       22.0       7.0         435 F       5.40       55.0       5.0       13.5       20.5       6.0         471 F       6.00       54.0       7.0       12.0       22.0       5.0         5.78       53.5       5.8       12.5       21.5       6.0	<b>M</b>	15470		00.9	57.0	0.9	8.5	23.5	5.0	3.10
431 F       5.95       51.5       5.5       12.0       22.0       7.0         435 F       5.40       55.0       5.0       13.5       20.5       6.0         471 F       6.00       54.0       7.0       12.0       22.0       5.0         5.78       53.5       5.8       12.5       21.5       6.0		HEAN		6.27	r.	4.7	•	24.8	0.9	3.47
435 F 5.40 55.0 5.0 13.5 20.5 6.0 471 F 6.00 51.0 7.0 12.0 22.0 5.0 5.78 53.5 5.8 12.5 21.5 6.0	4	15431		5.95	51.5	5.5	12.0	22.0	7.0	3,91
471 F 6.00 54.0 7.0 12.0 22.0 5.0 5.0 5.0	4	15435		5.40	55.0	5.0	13.5	20.5	0.9	2,00
5.78 53.5 5.8 12.5 21.5 6.0	4	15471		00.9	54.0	7.0	12.0	22.0	2.0	3.11
	KOUP A	MEAN		5.78	53.5	5.8	12.5	21.5	9•9	3.34

TABLE NO. 4 - URINE AWALYSIS PUREBREU BEAGLES RECEIVING WR149,024 AD (AX67287) FUR TWU WEEKS INITIAL

	SPERM	FEE	A A A A A A A A A A A A A A A A A A A	ள் அ	т п п п
	BACT	FEW MANY	FEW Many Many	3. 3. 3. 3. 3. 3.	in in
	BC WBC EPITH AMORPH CRYS BACT SPERM	MANY FEW MANY	т п я з	MANY MANY LITTLE FEW	MANY FEW FEW
	CROSCI EPITH	3-5	0-2 0-2 3-5	3 - 6 3 - 6 4 - 4	24 5 1 1 5 2 1 3
	N BC	0-3 2-6 0-1	0-2	1-3	1-3
	RBC	3-5			
	BILI- KUBIN		<b>0</b>	0	
•	PRO- TEIN	<b></b>	o+0		0
	ACE- TONE	200	000	000	000
	SU- GAR	-0-	<b>⊢</b> 00	0	0
	SP. CK.	1.053 1.053 1.055	1.036 1.020 1.016	1.055 1.035 1.021	1.06+ 1.055 1.025
	a I	991	951	0 m M	9 <b>-</b> 8
	νm×	EEE	TES	Z Z Z	Z Z Z
	AN I MAL NUNBER	15358 15348 15451	15359 15426 15454	15350 15448 15458	15377 15449 15459
	GRUUP NUMHER		200	m m m	4 4 4

IABLE NO. 4 - URINE ANALYSIS PUREBRED BEAGLES RECEIVING WRI49,024 AD (AX67287) FOR TWO WEEKS

	SPEKM	2 2 2 6 6 6 6 6 7 7 7	MANY	F E M M A N Y	MANY FEW FEA
	BACT	MANY FEW MANY	7 7 7 71 71 71 72 72 72	MANY MANY Fem	FEW MANY MANY
	HUINGS CRYS	MANY MANY MANY	MANY MANY MANY	N A B B B B B B B B B B B B B B B B B B	######################################
	MICKOSCUPIC FIRDINGS WBC EPITH AMORPH CRYS BACT SPEKM	LITTLE LITTLE MUCH	LITTLE MUCH	MUCH	LITTLË LITTLE
	ICKOSC EPITH	0-3	4-6	10-20 0-2 0-3	2-3 5-3 3-1
	WBC	3-2	0-3	0-2 0-3 0-5	5-7 0-3 0-1
-	RBC	0			
3. Tun X.	BILI- RUBIN	1 2 1			-0-
3 BUS	PKU- TEIN	<b></b>			<b></b>
	ACE- TONE	000	000	000	ာဂပ
	SU- GAR	000	10+		400
	SP • GR •	1.025 1.049 1.042	1.040 1.040 1.040	1.060 1.055 1.055	1.025 1.025 1.027
	O I	~ ~ ®	9 ~ ~	လ ပဲ သ	<b>~~</b> °
	SΜX	EXXE	TTT	ΣΣΣ	ZZZ
	AN IMAL NUMBER	1451 15358 15398 15398 15451	15359 15426 15454	15360 15448 15458	15377 15449 15459
	GROUP NUMBER		2 2 21	<b>ጣጠ</b> ጠ	<b>ታ</b> ታ ታ

- URINE ANALYSIS TABLE NO. 4

KS	SPERM	######################################	MANY Few Few	3 U.	7 F F 6 F F 8 7 3
O WEEKS	BACT	FEW MANY MANY	т. В 3	FEW MANY FEW	M A A A A A A A A A A A A A A A A A A A
FUR TWO	UDINGS CRYS	MANY MANY MANY	MANY MANY MANY	MANY MANY MANY	FEW MANY MANY
7287)	MICROSCOPIC FINDINGS	LITTLE MUCH	LITTLE	MUCH	LITTLE MUCH
ID (AX6	ICROSCO EPITH	1-2 3-4 3-5	1-2 3-4 3-4	3-4	3-4
8149,024 AD (	J	0-1 3-4 6-8	2-3 10-15	2-3	0 - 1 6 - 8
WR149	RBC	1-2	1-2		1-0
PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) WEEK 2	BILI- RUBIN	<b></b>	H ##	000	000
S REC	PRO- TEIN	<b></b>		00-	-0-
BEAGLE	ACE- TUNE	00	000	000	000
E0 (	SU- GAR	00		000	900
PUREBR	P H SP•GR•	1.035	1.048 1.041 1.042	1.011 1.016 1.040	1.020
	a I	<b>-</b> 9	~ 8 9	691	9~~
	SШX	III	EEE	TII	EXI
	AN I MAL NUMBER	15358 15398 15451	15359 15426 15454	15360 15448 15458	15377
	GROUP NUMBER	<b>~ ~ ~</b>	2 2 2	ጠጠጠ	444

TABLE NO. 4 - URINE ANALYSIS PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) FUR TWO WEEKS INITIAL

	SPERM				
	SBACT	### #### 333	FE MANY EANY	FEW MANY FEW	FEW
	IDINGS	MANY MANY FEW	F EW MANY MANY	FEW MANY MANY	MANY MANY MANY
	MICRUSCOPIC FINDINGSBC WBC EPITH AMORPH CRYS BACT SPERM			LITTLE	LITTLE
	CRUSC EPITH	2-6 0-1 0-1	0-2 1-2 0-3	3 - 4	0-3 0-1 4-6
	WBC	3-8		0-2 1-2 0-2	0-1
	KBC		3-4		
INITIAL	BILI- RUBIN	000	999	900	999
	PRU- TEIN		<b>9</b>	0	-0-
	ACE- TONE	000	000	000	000
	SU- GAR		<b>⊢</b> ⊶ <b>⊢</b>	0	
	SP. GK.	1.060 1.064 1.046	1.036 1.06+ 1.056	1.059 1.045 1.055	1.05¢ 1.05¢ 1.042
	a I	9 ~ ~	9 ~ ~	σσα	0 ~ ~
	NWX	TT IT	444	TT TT	<b>11.12.11.</b>
	ANIMAL NUMBER	15319 15432 15436	15322 15433 15437	15430 15434 15470	15431 15435 15471
	GROUP NUMBER		2 2 2	M M M	444

	1.5 1.5				
) 	SPERM				
	S BACT	MANY FEW FEW	### ### ###	# # # # # # \$ \$ \$	MANY
	DING: CRYS	MANY MANY MANY	MANY FEW MANY	MANY HANY MANY	FEW MANY
WEEK 1	MICROSCUPIC FINDINGS WBC EPITH AMORPH CRYS BACT	LITTLE	MUCH LITTLE MUCH	MUCH LITTLE LITTLE	
	CROSC EPITH	2-4 5-7 2-3	1-3	0-5 2-3 2-3	0-2
	WBC W	0-2	1-3 0-2 0-2	0-3 5-15 3-4	5-12 3-6
<b>-</b>	RBC				
1	BILI- RUBIN		-00	•••	00
	PRO- TEIN		<b>++0</b>		ပ၁
	ACE- TUNE	000	000	၁ပဝ	00
	SU- GAR	001	<b>⊢</b> ⊢ ⊢	-00	0 0
	SP • GR •	1.631 1.041 1.069	1.641 1.646 1.032	1.045 1.037 1.050	1.025 1.019
	a I	6 1 1	<b>√</b> 0 €C ±0	7 9 7	~ ~
	SHX	the the the	444	<b></b>	<u>u. u.</u> :
	AN I MAL NUMBER	15319 15432 15436	15322 15433 15437	15430 15434 15470	15431
	GROUP NUMBER		2 7 7	<i>ጠ</i> ጠ ጠ	44.

WO WEEKS	MICROSCOPIC FINDINGS	MANY FEN FEN	T T T T T T T T T T T T T T T T T T T	MANY FEW	ANAN
FUR TWO	INDING 1 CRYS	MANY MANY	FEE FEE MANY	FEW FEW MANY	Щ Э
57287)	PIC FI	MUCH			
VD (AXE	CROSC( EP I TH	1-2	2-3	3-4	3-5
YADLE NU. 4 - OKINE ANALYSIS S RECEIVING WR149,024 AD (AX6 WEEK 2	HBC	3-4	1-2	3-4	10-15
PUREBRED BEAGLES RECEIVING WR149,024 AD (AX67287) WEEK 2	RBC			2-3	2-3
CEIVING	BILI- RUBIN	000	000	000	0
S REC	PRO- TEIN	0 - 1	0 <b>-</b> -	0-1-	0
BEAGLE	ACE- TONE	000	000	000	0
(ED	SU- GAR	0	<del>-</del>	-0-	-
PUREBI	SP.GR.	1.020 1.041 1.06+	1.038 1.041 1.041	1.010 1.041 1.046	1.031
	a I		000		9
	SШX	<b></b>	444	<b></b>	u_
	AN I MAL NUMBER	15319 15432 15436	15322 15433 15437	15430 15434 15470	15431
	GROUP Number	and peop and	~~~	~ ~ ~	4

A China a Charles

Table No. 5 - TERAINAL BODY MEIGHTS, ORGAN MEIGHTS, AND URGAN/BODY MEIGHT KATIOS

SPECIES AND STRAIN — PUREASED REAGLES INTERVAL — TWO WEEKS MATERIAL — WE 149,624 AD ROUTE OF ADMINISTRATION — INTRAVENDUS

MALES - CUNTRUL

EN RATIO PCT	0.3034 0.2951 0.2297	0.2781		523
SPLEEN WEIGHT	42.700 30.100 25.500	32.767		
EK RATIÖ PCT	2.3116 2.3529 2.7000	2-4548	ES RATIG PCT	0.1906 0.1755 0.2468 0.2043
LIVEK WEIGHT G	319.000 240.000 299.700	280,233	TESTES WEIGHT G	26.360 17.900 27.460 23.367
RATIO PCT	0.4457 0.3294 0.9423	0.8725	MALS RATIU PCT	6.0086 0.0113 0.0135
HÉAKT WE LGHT G	116.700 84.600 104.600	101.967	ALKENALS WEIGHT K.	1.190 1.150 1.500
OLD RATIO PCT	0.0091 0.0093 0.0117	0.0100	KIDNEYS IT RATIO PCT	0.4848 0.4265 0.6681
THYROID Weight G	1.250 0.950 1.300	1.167	KIDN AEIGHT 3	66.400 43.500 67.500 54.300
TERM. RODY WEIGHT KG	13.80 10.20 11.10	11.70	TERM. UODY WEIGHT KG	13.30 10.20 11.15 11.70
AN I GAL	15358 15398 15451	MEAN	ANIMAL. NO.	15358 15398 15451 MEAN

The many many

Table No. 5 - Continued

## MALES - 5 MG/KG

ANIMAL	TERM. BODY	THYRU	010	HEAKT	IRT	LIVER	re R	SPLCEN	大山
NO.	HE LOHT KG	WEIGHT 6	RAT1U PCT	ME LGHT	RATIO PCT	мЕТGHT G	RAT IO PCT	we four	RATIO
15359	8.50	1.100	0.0129	71.360	6.8447	205.000	2.4118	21,300	0.250c
15456	11.50	1.200	0.0104	100.500	0.8739	235.000	2.0435	26.000	0.2261
15454	12.00	1.190	6600*0	114.200	1156.0	301,000	2,5083	24.400	0.2033
MEAN	13.57	1.163	0.6111	39¢*56	1088.0	247.000	2,3212	23.990	0.2207
ANIMAL	TERM. BODY	KIDNE	IEYS	AURENALS	IALS	FESTES	r. FS		
• CI &	WEIGHT KG	WEIGHT G	RATIO PCT	WEIGHT G	K4110 PC1	WEIGHT G	RATIO PCT		
15359	9€.×	36.200	95240	006.0	3.0106	15,500	0.2294		,
15+26	11.50	57.300	0.4983	1.400	0.0122	22,900	0.1991		5
15454	12.30	56.500	C.4875	1.930	0.6161	29,500	0.2456		24
MEAN	10.67	50.667	0.4765	1.410	9.0129	73.967	0.2248		l

MALES - 10 MG/KG

SPLEEN AT RATIU PLT	34.200 0.3353 21.300 0.2340 18.400 0.1756	24.033 0.2600		525	
SPI WEIGHT	34. 21. 18.	24.			
LIVER RATIU PCT	3.0698 2.6000 2.4951	2.7016	TES RATIU PCT	0.2275 0.3027 0.1951	Ü.2418
Нојак Гл	337.000 195.000 257.300	253.060	TESTES NEIGHT	23, 20 0 22, 700 23, 100	22,000
HEARI RATIO PCI	0.9451 0.9493 0.8748	0.9231	ADRĒNALS SHI RATĪG PCI	0.0130 0.0147 0.0135	0.0138
HEA SE LOHT G	96.466 71.200 90.100	85.900	ADRĒ WE IGHT G	1.330 1.100 1.400	1.277
THYKUID T KATIU PCT	0.0112 6.0160 0.0107	0.0126	NEYS RATIU PCT	0.6588 0.7013 0.4252	0.5951
WEIGH G	1.14C 1.203 1.103	1.147	KIUNEY WEIGHT G	67.200 52.600 43.800	54.533
TERM. BODY WEIGHT KG	10.20 7.50 10.30	9.33	TERM, BODY WEISHT KG	10.20 7.50 10.30	9.33
ANIHAL NG•	15300 15448 15458	MEAN	ANIMAL NO.	15448 15448 15458	MEAN

Table No. 5 - Continued

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SPLEEW IT RATIO PCT	330	0.2423		526
SPLE WE∫GHT G	44. 800 17.400 16.900	26.367		
/ER RATIU PCT	2.4609 2.8000 2.5467	2.6025	ES RATIU PCT	0.2696 0.1787 0.2027 0.1970
LIVER AFIGHT 6	243, 100 210, 000 191, 000	224.300	TESTES WEIGHT	24.100 13.400 15.200 17.567
HEAKI KATIO PCT	0.3c96 0.9733 0.9460	0.9276	JALS RATIU PCI	0.0133 0.0153 0.0153 0.0146
нЕ) ис 16н1 6	100.000 73.000 70.500	81.167	AUMENALS WEIGHT R.	1.50 1.150 1.150 1.267
tOID RATIJ PCT	0.3687 0.6144 0.6144	0.0125	EYS RATIU PCT	0.4157 0.6173 0.6400
THYROID WEIGHT RA	1.000 1.000 1.080	1,653	KIDNEYS WEIGHT K.	47.300 46.300 48.000 47.367
TEKM. BUDY AEIGHT KG	11.50 7.50 7.50	8. ¥.3	TERM. BODY WEIGHT KG	11.50 7.50 7.50 8.83
ANIMAL NU.	15377 15449 15459	MEAN	ANIMAL NO.	15377 15449 15459 MEAN

Table No. 5 - Continued

MALES -	CUNTRUL
MALE:	1
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i. L	ميلاء

ANIAL	TERM, BUDY	THYKE	_	HE	HEAGT	LIVER	F.X	NAT LON	5
•	110 1 3 M	1 Hr I H	RATIO PCI	1E31 = E	KATIU PCT	we IGHT G	RATIU PCT	WEIGHT 6	RATIO PCT
15319	12.40 9.60	1.200	0.0097 0.0099	78.160 08.400	0.6347 3.7u83	343.000 243.000	2.7661	20.000	0.1613
12426	٠٠٠ ١٠٠٥	0.4670	0.000	80.10C	6,8969	202,000	2-1042	32.000	0.3336
Pac 4:0	10.53	3.940	5800°0	77.000	0.7460	202.067	2.4072	28.200	0.2731
AMENAL NO.	TCRA. SHOY AFIGHT KG	KIONE MEI GHT G	SEYS RATIU PCT	ADAENALS NETSHT RES	ALS PATIU PCT				
15519 15432 15436	12.40 9.00 9.00	54.005 41.200 34.800	0.4403 0.4292 0.4042	1.300 1.400 1.450	0.0105 0.0146 0.0151				527
NEAN	10.53	44.867	0.4246	1.383	6.0134				

Table No. 5 - Continued

FEMALES - 5 MG/KG

EN RATIO PCT	0.3354 0.2737 0.1977	0.2706		528	
SPLEEN WEIGHT G	21,500 30,100 17,200	23.033			
ER RATIO PCT	2.1692 2.0556 2.7356	2,3201			
LIVER WEIGHT 6	141.000 222.000 238.000	200,333			
RI RATIU PCI	0.9154 0.8167 0.7747	Ü. 8356	ALS RATIU PCT	0.0132 0.0093 0.0115	0.0115
HEART WE LGHT G	59.500 88.200 57.400	71.700	ADRENALS WE IGHT	3.460 1.000 1.300	0.973
OID RATIU PCI	0.0108 0.0071 0.0071	0.0983	IEVS RATIU PCT	0.4277 0.3759 0.4678	0.4238
THYKÜI WEIGHT G	0.700 0.770 0.620	0.697	KIDNEYS WEIGHT KA	27.600 40.600 40.100	36,367
TERM. BODY WEIGHT KG	6.56 16.30 8.70	8.67	ТЭКМ. ВООУ AEIGMT KG	6.50 10.30 8.70	70.b
ANIMAL NU.	15522 15433 15437	MEAN	ANIFAL NU•	15322 15433 15433	7 H

Table No. 5 - Continued

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ANIMAL	TERM BUNY	THYRULU	0102	HE	HE AK T	-	ğ		
•	K G F G F F	WEIGHT G	RATIO PCT	WE IGHT 6	RATIU PCI	WFIGHT F	ER KATIO PCT	SPLEEN MEIGHF G	E.4 RATIO
15430 15434 15470	7.50 9.40 7.60	0.800 0.763 0.800	0.0107 0.0081 0.0105	65.900 76.200 67.500	0.3787 0.8100 0.8882	137.000 196.000 219.000	2.4933 2.0851 2.8816	16.500 22.500 20.230	0.2290 0.2394 0.2394
MEAN	8.17	0.787	9600*0	69.367	0.8592	200*602	2.4867	19.735	0.2417
ANIAAL NJ.	TERM. SUDY WEISHT KG	KIONEYS WEIGHT	EYS RATIU PCT	AURENALS WE IGHT KA G	IALS RATIU PCT				
15430 15434 15470	7.50 9.40 7.60	41.000 42.000 43.400	0.5467 0.4468 0.5711	1.280 1.150 1.200	6.0171 6.0122 9.0153				52
MEAN	0.17	42.133	6.5215	1.210	0.3150				9

Table No. 5 - Continued

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			-	LIMEES - CL MO/KG	5/ X/5					
ANINAL NO.	TeRM. BODY WEIGHT KG	THYKUI MEIGHT G	AUTD RATIO PCT	HEAKT WE LGHT 6	NRT RATIG PCT	LIVER WEIGHT 6	FER RATIU PCI	SPLEEN ME IGHT G	EN KATTJ PCT	
15431 15435 15471	7.30 6.00 8.20	0.890 0.490 0.830	0.0122 0.0082 0.0101	73.100 45.500 71.300	1.0014 0.7543 0.8695	206.000 145.000 149.000	2.6219 2.4167 2.4268	17.600 24.200 22.700	0.2411 0.4033 0.2763	
No.	7.17	0.737	0.0102	63,360	0.3764	183,333	2,5551	51.500	0.3071	
ANIMAL Ne.	TERM. BODY WEIGHT KG	KIDNEYS WEIGHT RA	JEYS RATIU PCT	ADRENALS WEIGHT RO G	ALS RATIU PCT					
15431 15435 15471	7 • 30 6 • 40 3 • 20	41.200 23.300 51.000	0.5644 0.4833 0.6220	1.000 0.920 1.390	0.0137 0.0153 0.0170				530	
MEAN	7.17	40.400	0.5506	1.103	0.0153					

## KEY FOR INCIDENCE TABLE

P = Present

N = No Section

A = Autolysis

X = Not Remarkable

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderately Severe/High

5 = Severe/High

	Groups 2 3 4	
Males	Animal N 15358 15398 15451 15426 15426 15426 15459 15377 15377 15459	
KIDNEY Interstitial nephritis Mineral deposit Tubular dilatation Papillary congestion Papillary epithelial hyperplasia Congestion Epithelial vacuolation	2 2 2 2	
STOMACH Glandular atrophy Dilatation of crypts Chronic gastritis	x x x	
PANCREAS Peripancreatitis	x x x x	
SMALL INTESTINE	x x x	
LARGE INTESTINE	x x x	
MESENTERIC LYMPH NODE	x x x	
URINARY BLADDER Cystitis Thickened epithelium Hydropic degeneration	x x x x	
TESTIS Epididymitis OVARY	x x x x	

OVARY Indeterminable activity

# DETAILED HISTOPATHOLOGY INCIDENCE TABLE

	:1						Gr	oup	s				
	S S	_	I			2			3	<del></del>		4	
	al	58	398	21	59	26	54	8	09	58	377	49	59
W-1	Animal	S	153	154	53	54	15454	154	15360	154	53	154	54
Males	اج		_			_			_				
ADRENAL		X	X	X							х	X	
Vacuolation/Z. Glomerulosa													2
Vacuolation/Z. Reticularis													
THYROID													
Parafollicular tissue		3	1	2	3	3	3			2			
Follicle size			3							3	2-		
Epithelial height Follicular epithelial		T	1 2	T	2	1	7		1 – : 2	21	1	1	3
vacuolation			-		-	•	~	-	-		-		•
Mineralization of colloid					1	1							
Cystic parathyroid Parafollicular cell								P	2		3		3
vacuolation								2	2		3		3
Focal parafollicular											P		
hyperplasia													
Lymphocytic thyroiditis													
HEART		X	X	X							X	X	X
Focal myocarditis													
SPLEEN													х
Extramedullary hematopoiesis		1											
Increase lymphoid activity Pigmentation											-	1	
R.E. Hyperplasia			1	3							4	1	
Siderotic nodule			P	•							P		
Green pigment/Malpighian													
corpuscles													
GALL BLADDER			X	X							X	X	X
Lymphocytic cholecystitis		1											
Focal lymphoid infiltration													
LIVER		x			X		x	X		X	X	X	х
Bile duct proliferation			1	2								_	
Bile plugs													
Hepatocyte vacuolation Congestion						2			1				
Lymphocytic pericholangitis						4			_				
-2													

	<u>i</u>	Groups	
Females	Animal N 15319 15432	15322 15433 N 15437 15430 15434 N 15430	15431 15435 15471
ADRENAL Vacuolation/Z. Glomerulosa Vacuolation/Z. Reticularis	2 1 3		1 2 1
THYROID  Parafollicular tissue  Follicle size  Epithelial height  Follicular epithelial  vacuolation  Mineralization of colloid  Cystic parathyroid  Parafollicular cell  vacuolation  Focal parafollicular  hyperplasia  Lymphocytic thyroiditis	2 32-3 2-32-32 1 1 1 2 1 3 1 P 1 2	2 2 2 1-22 2	2-32 3 11-21-2 3 3 2 2
HEART Focal myocarditis	x x 1		ххх
SPLEEN Extramedullary hematopoiesis Increase lymphoid activity Pigmentation R.E. Hyperplasia Siderotic nodule Green pigment/Malpighian corpuscles	1 1 1 3 1		1 1 3 2 1
GALL BLADDER Lymphocytic cholecystitis Focal lymphoid infiltration	1 X X	1	ххх
LIVER Bile duct proliferation Bile plugs Hepatocyte vacuolation	<b>X</b> 1	y x	X 1 P P
Congestion Lymphocytic pericholangitis	1		

		Grou	ps	
	<u> </u>	2	3	4
Males	Animal 15358 15398 15451	15359 15426 15454	15448 15360 15458	15377 15449 15459
BONE MARROW	хх			х
Pigment Increase cellularity Decrease cellularity	2			2 2
PITUITARY Cystic pars distalis				P

	Gro	ups
	<u>o</u> 1 2	3 4
Females	Animal 15319 15432 15436 15322 15433	15430 15434 15470 15431 15431 15431
KIDNEY Interstitial nephritis Mineral deposit Tubular dilatation Papillary congestion Papillary epithelial hyperplasia Congestion Epithelial vacuolation	2 2 2	111 111 111
STOMACH Glandular atrophy Dilatation of crypts Chronic gastritis	x 2 3	2 2 2
PANCREAS Peripancreatitis	x x	ххх
SMALL INTESTINE	x x x	ххх
LARGE INTESTINE	ххх	ххх
MESENTERIC LYMPH NODE	ххх	ххх
URINARY BLADDER Cystitis Thickened epithelium Hydropic degeneration	ххх	X X 1 2
TESTIS Epididymitis		
OVARY Indeterminable activity	<b>x x x</b>	X X

		Grou	ıps	
			3	4
Females	Animal 15319 15432 15436	15322 15433 15437	15430 15434 15470	15431 15435 15471
BONE MARROW Pigment Increase cellularity Decrease cellularity	ххх			х х 2

PITUITARY
Cystic pars distalis

TRW/

HAZLETON LABORATORIES

SPONSOR:

Walter Reed Army Institute of Research

DATE: Saptember 27, 1971

MATERIAL:

WR 149,024 AD (AX 67287)

LOT NO: 308/422

SUBJECT:

REPORT NO. 43

Subacute Intravenous Toxicity Study - Monkeys

Project No. 193-417

#### SUMMARY

WR 149,024 AD (AX 67287) was tested for subacute (two week) intravenous toxicity by injection into the saphenous vein of the hindlimb once daily, seven days a week, at dosage levels of 5, 10, and 20 mg/kg.

Aside from slight ataxia and decreased activity observed in five high level animals on one or two days only, all animals showed no indication of a compound-related effect with respect to the appearance and behavior of the animals.

Analysis of clinical laboratory data and ophthalmoscopic examinations revealed no compound-induced alterations. Gross necropsy and organ/body weight data was generally not remarkable.

Microscopic examination of tissue revealed no histopathological alterations attributable to the administration of the test material.



## OBJECTIVE

The purpose of this study was to evaluate the toxicity of WR 149,024 AD (AX 67287) following intravenous injection daily, seven days a week, for two weeks.

#### MATERIAL

<u>Identification</u> WR 149,024 AD (AX 67287); Lot No. 308/422.

Description White powder.

Receipt Date May 12, 1971.

Purity Assumed 100% active ingredient.

## **METHODS**

## Experimental Animals

Breed: Young rhesus monkeys.

Number: Twelve males and 12 females.

Body Weight (At Initiation): From 2.3 to 3.8 kg.

Housing: Individually in metal cages.

Diet: Purina Monkey Chow twice daily, fresh fruit daily, and water ad libitum.



## Groups and Dosage Levels

Group No.	No. of Animals	Dosage Levels
	male female	mg/kg of body weight
1 (Control)	3 3	0
2	3 3	5.0
3	3 3	10.0
4	3 3	20.0

# Compound Administration and Preparation

The compound was mixed with isotonic saline at a concentration of 20 mg/ml and injected once daily, seven days a week, for two weeks into the saphenous vein of the hindlimb.

### Observations and Records

Daily: Appearance, behavior, appetite, elimination, and pharmacotoxic signs.

Weekly: Body weight.

## Clinical Studies

Performed: Initially and at one and two weeks.

Hematology: Hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte count, and clotting time.

Clinical Biochemistry: Fasting blood sugar, blood urea nitrogen, total serum protein, total serum bilirubin, serum albumin, serum potassium, serum chloride, carbon dioxide, serum calcium, serum glutamic-pyruvic transaminase, serum alkaline phosphatase, serum glutamic-oxaloacetic transaminase, and serum electrophoresis.



Urine Analysis: Specific gravity, pH, glucose, ketones, total protein, bilirubin, and microscopic examination of sediment.

# Ophthalmologic Examination

Performed on monkeys intially and at termination.

### Terminal Studies

Terminal Sacrifice: By exsanguination under anesthesia after 18 days.

Gross Necropsies: On all sacrificed monkeys.

#### Tissue Preservation:

In 10% Neutral Buffered Formalin - Brain, pituitary, thoracic spinal cord, eye, thyroids, lung, heart, liver (two lobes), gallbladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, prostate, testes, skin, rib junction, bone marrow, nerve with muscle, unusual lesions, and infection sites.

Organ Weights for Each Monkey - Thyroids, heart, liver, spleen, kidneys, adrenals, testes with epididymis, and ovaries.

#### Histopathological Examination

From Control and High Level Animals: Sections of brain, thoracic spinal cord, thyroids, heart, liver, gallbladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testes, ovary, and bone marrow.

From Low and Intermediate Level Animals: Liver, kidneys, and unusual lesions.

#### RESULTS

# Appearance, Behavior, and Signs of Compound Effect

Individual weekly body weights are presented in Table No. 1.

Ataxia and decreased activity immediately after dosing was observed on one or two days in five high level animals. However, these animals appeared generally normal, otherwise, as did all animals at the intermediate and low level. Monkey No. 892 showed depression, salivation, and watery emesis immediately postdose on Day 12.

Incidental findings observed in several animals from each group including the control were anorexia, soft feces or diarrhea, piloerection, and rough haircoat. Body weight gains were similar between control and test animals.

## Clincial Studies

The results of the clinical studies on individual animals are presented in Tables No. 2 (hematology), No.3 (blood chemistry), and No. 4 (urine analysis).

Hematological data revealed no significant trends attributable to the consumption of the compound. Decreased white blood counts were observed in one Group No. 2 and one Group No. 3 level animal at two weeks.

Blood chemistry findings, likewise, indicated no signs of compound-induced alterations. Incidental findings included elevated blood urea nitrogen counts at two weeks in one control, one low, and one high level animal. High alkaline phosphatase values noted at one week in one control female, two low level females, one intermediate level male, and three high level males had returned to normal levels by Week 2.

### Eye Examinations

Eye examinations were performed using Mydriacyl as a mydriatic, a binocular magnifier, a direct ophthalmoscope, and a binocular indirect ophthalmoscope while the animals were lightly anesthetized with Sernylan. No gross ocular changes were observed initially or at termination.

### Gross Necropsy

No alterations were noted which were directly related to administration of the compound. Alterations noted in the control group included large intestines adherent to the abdominal wall (Monkey No. 908H) and a white elevated area in the stomach mucosa (Monkey No. 912H). Control Monkey No. 787H showed small thyroids, a swollen spleen, and cystic ovaries with the right ovary larger than the left.

Alterations observed in the low level group included an elevated area in the stomach mucosa measuring 2.5 cm. x 1.5 cm. in Monkey No. 925H, and a swollen spleen in Monkey No. 909H. In Monkey No. 913H, the left cerebral hemisphere had an oblique cavity located at the midline and extending ventrally into the parenchyma. The lesion was lined with a brownish, necrotic-looking material.

In the intermediate level group, Monkey No. 892H showed a granular-appearing spleen.

Adhesions from the lung to the pleura or signs of parasitic infestation were observed in all groups including the control and are routinely observed signs in laboratory primates.

### Organ Weights

Individual terminal body weights, organ weights, and organ/body weight ratios are found in Table No. 5.

Incidental variations from normal ranges included a high ovary/body weight ratio in one control female (Monkey No. 787H), a high adrenal/body weight ratio in one intermediate female (Monkey No. 797H), and a high thyroid/body weight ratio in one high level female (Monkey No. 923H).

### Microscopic Pathology

The daily intravenous injection of WR 149,024 AD (AX 67287) for a period of 14 consecutive days to male and female rhesus monkeys at the rate of 5.0, 10.0, and 20.0 mg/kg of body weight did not result in the production of any compound-related histopathological alterations in the tissues examined. Incidental lesions were seen in several of the organs examined, but the incidence and severity of these changes in the test animals were not meaningfully different from that of the controls.

The thyroid activity in the male control monkeys varied from slight to moderate. Similarly, the activity of the thyroid in the male monkeys receiving 20.0 mg/kg/day varied from slight to moderate. In the females, the activity of the thyroid was also slight to moderate in both the controls and in the animals receiving 20.0 mg/kg of body weight per day.

Scattered incidences of cortical and medullary mineralization were seen in the adrenals from both the control and test monkeys. The incidence of this microscopic finding was slightly greater in the female control and test animals than in the males.

Pericholangitis was a frequent finding in all groups, but in no case was it greater than slight in severity. Some variation in the degree of hepatocyte vacuolation was noted among individual animals in both the control and test groups. This microscopic observation was not consistent and was not seen any more frequently in the test animals than the controls.

Lesions associated with parasite infestation were seen in the mesenteric lymph nodes and on the serosal surfaces of the large and small intestines. Occassionally the parasite was present in the lesion, but more frequently it was absent. Pancreatitis was seen in Group No. 4 female

Monkey No. 917H. This inflammatory lesion was characterized by an infiltration of mononuclear macrophages, lymphocytes, and some polymorphonuclear granulocytes into the parenchyma of the pancreas. The acinar cells of the affected lobules appeared to be undergoing a degeneration which was characterized by a loss of zymogen granules, cytoplasmic vacuolation, and slight nuclear vesiculation.

The capsule of the pancreas in this area was severely thickened, and there was hyperplasia of fibrous connective tissue throughout the lobule.

In conclusion, it can be stated that the daily intravenous injection of WR 149,024 AD (AX 67287) for a period of 14 days to male and female rhesus monkeys at a dosage rate of up to 20.0 mg/kg does not cause any histopathological

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alterations in the tissues examined on this study. With the exception of scattered instances of parasitic disease and a few instances of chronic infections, the organs were generally within the limits of normal histological variation.

Submitted by

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Pachology by

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Report Preparation: Horwatt Supervision: R. Thompson

dc;gbb

NOTE: The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

## EXPLANATION OF FOOTNOTES

Key to urine analysis table is as follows:

- 0 = negative
- $T = trace (\pm)$
- 1 = slight (+)
- 2 = moderate (++)
- 3 = marked (+++)
- 4 = severe (++++)

V T L YEL = very turbid light yellow

T D YEL = turbid dark yellow

Table No. 1 - Individual body weights for rhesus monkeys receiving WR 149,024 AD (AX 67287)

TIME	MONKEY NO. 900H M MONKEY NO.	1 18	908H M MONKEY NO. 912H M MONKEY N	MONKEY NO. 787H F	MONKEY NO. 80411 F	MONKEY NO. 930H F
Veeks	WEIGHT.	kg.	WEIGHT kg.	WEIGHT kg.	WEIGHT	WEIGHT
Initial	2.4	3.0	3.8	3.1	2.7	2.5
1	2.2	3.0	3.9	3.1	2.8	2.6
7	2.5	2.9	4.0	3.1	2.9	2.6
Terminal	2.6	2.7	4.1	3.2	2.9	2.6
Net Change, kg.	e, +0.2	.0	+0.3	<del>1</del>	Ş	- -
						548

Table No. 1 - Continued

		GROUP N	RROUP NO. 2 - 5.0 MG/KG OF BODY WEIGHT LEVEL	BODY WEIGHT LEVEL		
TIME	MONKEY NO. 889H M MONKEY NO. 8 WEIGHT WEIGHT	MONKEY NO. 891H M WEIGHT	891H M MONKEY NO. 909H M MONKEY NO. 799H F WEIGHT	MONKEY NO. 799H F WEIGHT		MONKEY NO. 913H F MONKEY NO. 925H M
weeks	· 8y	kg.	kg.	k8.	kg.	kg.
Initial	3.0	2.5	2.3	3.1	2.6	2.9
-	3.1	2.6	2.4	2.9	2.6	2.9
7	3.1	2.7	2.5	3.2	2.6	3.0
Terminal	3.2	2.6	2.4	3.1	2.6	3.0
Net Change, kg.	e, +0.2	+0.1	+0.1	0	0	+0.1

Table No. 1 - Continued

TDE	MONKEY NO. 881H M MONKEY NO.	MONKEY NO. 894H M	MONKEY NO. 897H M	894H M MONKEY NO. 897H M MONKEY NO. 797H F	MONKEY NO 8021 P	MONKRY NO 8030 & MONKRY NO 00000
INIEKVAL	WEIGHT	WEIGHT	WEIGHT	WEIGHT	THISTER IN	MONET NO. SUCH F
	K8.	kg.	kg.	kg.	kg.	WEIGHT
Initial	2.6	2.8	2.9	2.6	3.4	, e
-	2.7	2.9	3.1	2.6	3.5	er,
7	2.7	3.0	3.2	2.6	3.6	, e.
Terminal	2.8	3.1	3.3	2.6	3.5	) e
Net Change, kg.	+0.2	+0.3	4.0+	0	Ę.	

Table No. 1 - Continued

			GROUP NO. 4 - 20 MG/MG OF RODY WETCHT I BUET	RODY UPICHT I BUDY		
TIME	MONKEY NO. 892H M MONKEY NO.		895H M MONKEY NO. 911H M MONKEY NO. 807H F	MONKEY NO. 807H F	MONKEY NO 917H F	MONEY NO 0228 E
INTERVAL	WEIGHT		WEIGHT	WEIGHT	WEIGHT	
Weeks	к8.	kg.	kg.	kg.	kg.	kg.
Initial	2.5	2.7	3.1	2.9	2.9	3.1
-	2.6	2.7	3.2	2.9	3.0	3.1
7	2.3	. 2.8	3.3	3.0	3.0	3.2
Terminal	2.2	2.8	3.3	3.1	3.0	3.2
Net Change, kg.	.e. -0.3	+0.1	+0.2	+0.2	+0.1	10.1

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHESUS MONKEYS RECEIVING WK 149,024 AD (AX67287) FOR TWO WEEKS
INITIAL

		S					1		DIFFE	DIFFERENTIAL			
GROUP	ANIMAL NUMBER	w×	HCT **	HGB	RBC MILLS	WBC	ME TA		SEG.	LYMPH	HONO	EOS IN	BASU
~	H006	×	36.0	13.0	5.01	8	0	0	35	61	7	2	0
-	H806		39.0	12.8	5.40	12.6	0	0	28	04	-	0	~
	912H		41.0	14.2	5.36	8.5	0	0	54	43	7	0	-
GROUP	MEAN		38.7	13.3	5.24	<b>9</b> •8							
7	<b>889H</b>	Σ	40.0	13.8	5.54	14.3	0	0	20	76	m	-	0
7	<b>891</b> H	I	40.0	13.9	5.61	4.9	0	0	25	42	-	0	0
7	H606	I	37.5	12.7	5.43	9.7	0	0	54	43	0	7	7
GROUP	MEAN		39.2	13.5	5.53	10.1							
ю	881H	τ	41.5	13.8	5.69	9.1	0	0	45	54	ю	-	0
m	894H	I	39.5	13.4	5.42	8.0	၁	0	41	54	၁	S	0
6	897H	x	37.0	13.4	5.72	7.2	0	0	39	65	7	-	0
GROUP	MEAN		39.3	13.5	5.61	8.1							
4	892H	Σ 1	39.0	13.4	5.48	11.9	00	00	<b>51</b>	80	~	7 -	90
14	H116	E	38.5	13.0	5.09	8.7	00	0	43	5, 5	• 0	<b>-</b>	7 7
ROUP	GROUP MEAN		39.5	13.6	5.52	10.9							

TABLE NU. 2 - INDIVIDUAL HEMATOLOGICAL VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS

Ċ		v					1 1 1 1	1 1 1 1 1	OIFFE	-DIFFERENTIAL-			
GKCO P NUMBER	ANIMAL R NUMBER	ш×	HCT #	HGB	RBC MILLS	WBC	ME TA	BAND *	SEG.	LYMPH %	MONO	EOS IN	BAS0
-	H006	I	37.0	12.3	4.92	8.6	0	0	51	46	-	8	0
_	908H		39.0	11.8	4.96	13.6	0	0	58	45	0	0	0
~	912H	Z	37.5	11.8	4.35	9•9	0	0	35	64	0	-	0
OUP	GROUP MEAN		37.8	12.0	4.14	9.6							
7	H688	X	39.5	12.3	5.01	9.7	0	0	54	16	0	0	0
7	891H		38.0	12.8	5.05	6.2	0	0	57	42	-	0	0
7	H606		35.0	11.8	5.20	6.2	0	0	37	19	-	-	0
OUP	GROUP MEAN		37.5	12.3	5.09	7.4							
m	881H	I	38.0	11.9	4.83	13.1	0	0	55	41	6		0
æ	894H		36.0	11.9	4.91	5.8	0	0	52	43	0	7	0
m	897H		35.0	11.6	4.70	5.9	0	0	53	45	0	7	0
COUP	GROUP MEAN		36.3	11.8	4.81	8•3							
4	892H	I	39.0	12.7	5.20	15.5	0	0	69	59	7	0	0
4 4	895H 911H		41.0 37.0	13.4 11.9	5.54 4.57	8.8 11.3	00	00	36 62	62 38	-0	-0	00
SOUP	GROUP MEAN		39.0	12.7	5.10	11.9							

GROUP		HCT	T HGB	RBC	78 <u>*</u>	META	BAND	OIFFEF SEG	DIFFERENTIAL-BAND SEG LYMPH	NONO	EOSIN	BASO
NUMBER	NUMBER X			MILLS	THS	*	<b>34</b>	<b>34</b>	<b>»</b>	<b>»</b>	×	<b>54</b>
	M H006	1 39.0	0 12.8	5.20	8.4	0	0	19	37	0	7	0
			_	5.16	21.1	0	0	69	27	~	M	0
-	912H M		0 13.0	4.80	7.6	0	0	55	44	<b>~</b>	-	-
GROUP MEAN	HEAN	39.0	0 12.7	5.05	12.4							
7	M H688	0.44	13	5.24	14.8	0	0	48	84	7	2	0
7			13.	5.36	8.2	0	0	64	20	0		0
7	₩ H606	35.0	0 12.5	5.35	12.5	0	0	7.1	53	0	0	0
GROUP MEAN	HEAN	39.7	7 13.2	5.32	11.8							
m	881H M	36.0	11.	4.70	15.2	0	0	61	35		m	0
m			12.	5.05	4.9	0	0	31	19	0	7	0
m	897H M		11.	5.03	5.8	0	0	41	52		0	0
GROUP MEAN	HEAN	36.0	11.8	4.93	8.6							
4	892H M		12.	5.43	18.3	0	0	09	36	m	-	0
4	895H M	37.0	12.7	5.25	9.5	0	0	52	14	0	-	0
4	911H H		11.	4.70	11.0	0	0	70	30	0	0	0
GROUP MEAN	HEAN	37.7	7 12.4	5.13	12.8							

TABLE NO. 2 - INDIVIDUAL HEMATULOGICAL VALUES RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEE

		S							DIFFE	DIFFERENTIAL-		*	
GROUP	ANINA		¥CT	HGB	R8C	WBC	ME TA	BAND	SEG	LYMPH	MONO	EOS IN	BASO
				Š	41113	Ç <u>E</u>	•	•	•	•	•	•	•
-	787H	<b>L</b>		12.7	5.14	7.5	0	0	22	89	٣	_	0
-	804H	<b>L</b>				13.6	ပ	0	21	69	4	9	၁
-	930H	T	40.5			7.7	0	0	64	64	-	7	0
GROUP	MEAN		39.5	13.2	5.16	9.6				-			
7	779H	T.		12.5		13.8	0	0	39	58	7	-	0
7	913H	<b>L</b>	40.0	14.2	5.44	4.5	0	0	20	16	7	7	0
7	925H	L T		13.6		17.1	0	0	55	36	0	6	0
GROUP	MEAN		39.8	13.4	5.43	11.8							
m	H161	T .		13.4		11.3	0	0	64	48	-	-	-
6	802H	<b>L</b>	36.0	12.7		11.8	0	0	23	72	ß	٥	0
m	Н908	<b>+</b>		13.4	5.26	7.7	0	0	45	53	7	m	0
GROUP	MEAN		38.5	13.2	5.10	10.3							
4	805H	T.		13.9		8.2	0	0	43	20	4	m	0
4	917H		44.0	14.6	6.13	7.1	0	0	<b>5</b> 6	69	က	-	-
4	923H	ц Т		13.2		16.0	0	0	34	09	æ	7	-
GROUP MEAN	MEAN		41.7	13.9	5.59	10.4							

		v					1	1	DIFFE	DIFFERENTIAL	1		
GROUP	AN I MAL	<b>м</b> ×	¥C1	HGB GM#	RBC MILLS	WBC	META %	BAND	SEG.	LYMPH *	MON S	EOS IN	BASO
-	787H	u	36.5	11.6	4.61	6.7	0	0	64	64	0	7	0
• ~-	804H		36.5	11.9	4.75	11.2	0	0	39	57	~	m	0
-	930H		43.0	13.4	5.08	6.7	0	0	52	44	0	-4	0
GROUP	MEAN		38.7	12,3	4.81	8.2							
7	199H	u.	34.0	11.1	4.44	11.3	0	0	69	28	2	-	0
7	913H	u.	38.0	12.5	4.66	4.1	0	0	31	69	0	0	0
7	925H		40.0	12.5	5.25	12.8	0	0	99	34	0	0	0
GROUP	MEAN		37.3	12.0	4.78	<b>9.6</b>							
~	797H	u	39.0	12.5	4.65	7.7	0	0	43	55	~		0
m	802H		37.5	11.9	4.54	10.7	0	0	35	65	0	0	0
m	806н	u.	40.0	13.0	4.91	7.4	0	0	65	35	0	0	ပ
OUP	GROUP MEAN		38.8	12.5	4.70	8.6							
4	807H	ų.	36.0	12.1	4.65	15.1	Ö	0	99	36	0	0	0
4	917H	u.	38.5	12.7	5.37	6.2	0	0	58	41	0	<b>,</b>	0
4	923H	u.	37.0	11.8	4.14	8.2	0	0	38	09	~	-	0
GRUUP	Z.		37.2	12.2	4.92	9.8							

		v								TELEBORY I AL			
1 1 1 ROUP MEA	ANIMAL	жшх	ĦĊŢ	HGB GM\$	RBC MILLS	WBC		1	SEG **			EOSIN	BAS0
1 1 ROUP MEA	787H	u.	38.0	12.7	5.12	8.2	0	0	55	74	c	-	C
1 Roup mea 2	804H		39.0	13.4	5.44	11.7	0	0	26	. 69	0	٠	- (
ROUP MEA	930H	u.	44.0	14.6	5.47	8.1	0	0	49	41	-	ım	0
2	Z		40.3	13.6	5.34	9,3							
	<b>199H</b>	u	39.0	12.8	5.08	18.2	0	0	74	54	0	٥	C
2			37.0	12.8	4.81	4.9	0	0	42	56	-	) <del></del>	· C
		ų.	38.0	12.8	5.38	15,3	0	0	19	35	ı ,	٠.	7
GROUP MEAN	Z		38.0	12.8	5.09	12.8							
6	<b>H</b> 267	u.	37.0	11.9	4.76	8.0	0	0	50	04	c	-	c
3		u	38.0	12.3	4.83	7.6	0	0	20	7.7	· -	• ^	) C
6		u.	39.0	13.0	5.07	11.2	0	0	2	53	• 0		0
GROUP MEAN	×		38.0	12.4	4.89	8.9							
4		u.	36.0	12.1	4.93	11.0	0	0	9	40	0	0	G
4		<u>u</u>	41.0	13.0	5.74	6.5	0	0	35	65	0	0	0
4	923H	L.	36.0	11.6	4.75	13.0	0	0	19	31	0	7	0
GROUP MEAN	z		37.7	12.2	5.14	10.2							

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES RHESUS MUNKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS

( A X 6 / 2 8 / 1									
149,024 AD	ATION SEC	47 58 19	21	19 47 31	32	23 56 50	43	13 08 17	13
WK 149	COAGULATION MIN SEC	ቁጠቁ	*	444	4	444	4	444	4
	νшх	III		III		III		EIE	
RECEIVING INITIAL	ANI MAL NUMBER	900H 908H 912H	MEAN	889H 891H 909H	MEAN	881H 894H 897H	MEAN	892H 895H 911H	MEAN
MUNKEYS	GROUP	, ma , ma	GROUP	222	GROUP	m m m	GROUP	444	GROUP
ESUS									

TABLE NO. 2 - INDIVIDUAL HEMATOLUGICAL VALUES RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS WEEK 1

ATION SEC	4 4 6 6 8 4 8 8 8 8 8 8 8 8 8 8 8 8 8 8	44	26 15 12	18	30 42 45	39	56 06 19	07
CUAGULATION MIN SEC	<b>m</b> m m	ю	m m m	æ	๓๓๓	æ	N M M	æ
νшх	X Z Z		III		III		III	
. ~								
ANI MAL NUMBE R	900H 908H 912H	IEAN	899H 891H 909H	EAN	861H 894H 897H	EAN	892H 895H 911H	EAN
GROUP ANIMAL NUMBER NUMBER	1 900H 1 908H 1 912H	GROUP MEAN	2 889H 2 891H 2 909H	GROUP MEAN	3 861H 3 894H 3 897H	GROUP MEAN		GROUP MEAN

19

GROUP MEAN

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS WEEK 2

COAGULATION Min sec	3 15 3 29 3 25	3 23	3 18 3 22 3 10	3 17	3 07 3 39 3 22	3 23	3 51 3 05 3 02	
ANIMAL E NUMBER X	900H M 908H M 912H M	MEAN	889H W 891H W 891H W 909H W	MEAN	881H M 894H M 897H M	MEAN	892H M 895H M 911H M	
GROUP		GROUP	777	GROUP	ммм	GROUP	444	

TABLE NO. 2 - INDIVIDUAL HEMATULOGICAL VALUES RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS Initial

ATION SEC	00 08 49	61	54 45 47 47	18	27 46 41	18	44 30 22	12
COAGULATION Min Sec	4 rv w	4	44m	4	440	4	m 4 4	4
s m x			4		<b>LL 1L</b> LL		<b>u.</b> u. u.	
ANI MAL NUMBER	787H 804H 930H	MEAN	779H 913H 925H	MEAN	797H 802H 806H	MEAN	805H 917H 923H	MEAN
GROUP NUMBER		GROUP A	000	GROUP M	ммм	GROUP M	444	GROUP M

TABLE NO. 2 - INDIVIDUAL HEMATOLOGICAL VALUES RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS WEEK I

ATION	00 10 59	03	14 15 20	16	20 28 10	19	45 45 39	23
COAGULATION MIN SEC	m m N	6	๛๛๛	69	ммм	3	m W m	3
νшх	<b></b>		444		u. u. u.		444	
ANI MAL NUMBER	767H 804H 930H	MEAN	799H 913H 925H	MEAN	797H 802H 806H	MEAN	807H 917H 923H	MEAN
GROUP		GROUP	888	GROUP	៣៣៣	GROUP	444	GROUP

.UES FOR TWO WEEKS E H

UAL HEMATOLOGICAL VALL 149,024 ad (ax67287) f	COAGULATION Min sec	3 14 3 00	3 11	3 03 3 25 3 15	3 14	3 45 2 50 3 03	3 13	3 35 3 12	60
VIO WR		<b></b>		עב עב עב		<b>LL LL LL</b>		Ա. Ա. <u>Մ</u> .	
2 T RECEIV WEE	ANIMAL	787H 804H 930H	MEAN	799H 913H 1 925H	MEAN	797H 802H 806H	MEAN	807H 917H 923H	MEAN
TABLE NO. Hesus Monkeys	GROUP NUMBER	# FF #	GROUP	888	GROUP	ммм	GROUP	444	GROUP

) WEEKS - INDIVIDUAL BLOOD CHEMISTRY VALUES TABLE NO. 3

			KHES	SUS MO	NKEYS R	RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287)	149,024 AU	(AX67287)	FUR TWO	2
GROUP NUMBER	AN IMAL R NUMBER	νшх	GLUCOSE MG%	BUN	SGPT R-F•	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MGZ	SGOT K.UNITS		
	900H 908H 912H	EEE	95.0 92.0 99.0	15.0 11.0 15.0	31.0 29.0 28.0	45.0 25.0 49.0	0.31 0.30 0.40	49.0 52.0 45.0		
GROUP	MEAN		95.3	13.7	29.3	39.7	0.34	48.7		
888	889H 891H 909H	Z Z Z	90.0 92.0 83.0	13.0 17.0 11.0	35.0 36.0 31.0	43.1 39.0 86.4	0.31 0.40 0.31	53.0 55.0 42.0		
GROUP	MEAN		88.3	13.7	34.0	56.2	0.34	50.0		
m m m	881H 894H 897H	EEE	89.0 106.0 92.0	15.0 11.5 16.0	34.0 31.0 31.0	48.0 81.6 40.1	0.39 0.38 0.40	58.0 56.0		
GRUUP MEAN	MEAN		7.56	14.2	32.0	56.6	0,39	55.0		
444	892H 895H 911H	III	82.0 94.0 85.0	13.0 17.0 14.0	28.0 38.0 32.0	73.6 81.6 48.0	0.30 0.49 0.30	56.0 57.0 48.0	-	
GROUP MEAN	MEAN		87.0	14.7	32.7	1.19	0.36	53.7		

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS

GROUP		<b>-</b> ,	→ ,	<b>,1</b>	GROUP	8	2	~	GROUP	<b>.</b>	ki.	m	GROUP	4	4	4	GROUP MEAN
ANIMAL E		X H006	N H806	912H M	MEAN	889H M	W H168	N H606	MEAN	881H M	894H M	897H M	MEAN	892H M	895H M	911H H	MEAN
GLUCUSE	<b>*</b>	86.0	110.0	115.0	103.7	89.0	90.0		89.7	86.0	84.0	0.66	89.7	104.0	126.0	104.0	111.3
S C		22.0	15.0	28.0	21.7	20.0	27.0	13.0	20.0	21.0	16,5	23.0	20.2	21.0	20.0	25.0	22.0
SGPT	¥-	25.0	31.0	38.0	31.3	38.0	39.0	35.0	37.3	36.0	35.0	39.0	36.7	36.0	41.0	41.0	39•3
ALK. PHOS	K-A. UNI I S	82.8	33.2	106.8	74.3	92.0	39.0	121.6	84.2	49.0	150.0	45.2	80.4	121.6	153.2	136.8	137.2
BIL IRUBIN TOTAL	M U E	0,31	0.29	0° 39	0•33	0° 30	0.28	0° 30	0, 29	0° 30	0.21	0.29	0.27	0.38	0.34	0.30	0.34
SGOT	K. UNITS	57.0	46.0	48.0	50.3	51.0	50.0	39.0	46.7	46.0	44.0	49.0	46.3	52.0	53.0	57.0	54.0

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 2

S GLUCOSE BUN SGPT ALK.PHOS X MG\$ MG\$ R-F. K-A.UNITS	900H M 105.0 908H M 86.0 912H M 116.0
BUN SGPT ALK.PHOS MGZ R-F. K-A.UNITS	
SGPT ALK.PHOS R-F. K-A.UNITS	
ALK.PHOS K-A.UNITS	27.0 19.0 35.0
S	27.0 27.0 28.0
_	68.0 39.0 71.2
BILIRUBIN TOTAL MGC	
SG0T K. UNITS	0.30 0.39 0.39

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS

GROUP         ANIHAL         CLUCOSE         BUN         SGPT         ALK.PHOS         TOTAL HGZ         SGOT K.UNITS           1         787H         76.0         15.0         35.0         79.2         0.39         58.0           1         804H         79.0         15.0         36.0         56.0         0.39         58.0           GROUP         MEAN         80.0         15.0         36.0         45.2         0.30         56.0           CROUP         MEAN         80.0         16.3         35.0         45.2         0.36         56.0           GROUP         MEAN         86.0         12.0         32.0         45.2         0.36         56.0           GROUP         MEAN         86.7         12.3         34.0         46.0         0.34         56.0           GROUP         MEAN         86.7         12.3         34.0         46.0         0.34         56.0           GROUP         MEAN         72.7         12.7         33.7         53.0         0.30         62.3           GROUP         MEAN         72.7         12.7         33.7         53.0         0.39         62.0           4         923H F <t< th=""><th></th><th></th><th></th><th>Z HE</th><th>SUS MG</th><th>INKEYS</th><th>RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR T INITIAL</th><th>149,024 AD</th><th>(AX67287) F</th><th>98</th></t<>				Z HE	SUS MG	INKEYS	RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR T INITIAL	149,024 AD	(AX67287) F	98
B7H F       76.0       15.0       35.0       79.2       0.39         194H F       79.0       15.0       36.0       65.6       0.39         130H F       85.0       16.3       35.0       61.3       0.36         13H F       75.0       13.0       32.0       45.2       0.36         13H F       75.0       13.0       32.0       45.2       0.36         13H F       75.0       13.0       32.0       49.9       0.40         25H F       100.0       8.0       32.0       49.0       0.36         97H F       69.0       12.3       34.0       48.0       0.36         02H F       80.0       12.0       38.0       46.0       0.36         06H F       69.0       12.0       38.0       46.0       0.30         12.7       12.7       33.7       53.0       0.30         17H F       66.0       11.0       32.0       46.8       0.30         17H F       66.0       11.0       34.0       46.8       0.30         17H F       66.0       11.0       32.0       46.8       0.30         17H F       66.0       11.0       32.0	GROUP NUMBER			GLUCOSE	BUN	SGPT R-F.		BILIRUBIN TOTAL MG#	SGOT K. UNITS	
130H F 85.0 19.0 34.0 39.0 0.40  19 80.0 16.3 35.0 61.3 0.36  19 9H F 85.0 16.0 32.0 45.2 0.30  13 H 7 75.0 13.0 38.0 49.9 0.40  25 H 7 100.0 8.0 32.0 49.9 0.31  86.7 12.3 34.0 48.0 0.34  97 H 69.0 12.0 38.0 46.0 0.30  02 H 7 80.0 14.0 32.0 68.0 0.30  02 H 80.0 12.0 38.0 46.0 0.30  17 12.7 12.7 33.7 53.0 0.32  17 12.7 33.7 53.0 0.29  17 1 2 11.7 31.3 58.5 0.30	~ ~	787H 804H		76.0	15.0	35.0		0.39	58.0	
99H F 85.0 16.0 32.0 45.2 0.36 13H F 75.0 13.0 38.0 49.9 0.40 25H F 100.0 8.0 32.0 49.0 0.31 86.7 12.3 34.0 48.0 0.34 97H F 69.0 12.0 38.0 46.0 0.30 02H F 80.0 12.0 32.0 68.0 0.30 05H F 69.0 12.0 31.0 44.9 0.30 17.7 12.7 33.7 53.0 0.33 23H F 65.0 15.0 34.0 43.0 0.29 17H F 64.0 11.0 32.0 46.8 0.31 23H F 85.0 13.3 58.5 0.30	-	H066		85.0	19.0	34.0		0.40	08°0 65°0	
99H F 85.0 16.0 32.0 45.2 0.30 25H F 100.0 8.0 32.0 49.9 0.40 25H F 1000.0 8.0 32.0 49.0 0.31  86.7 12.3 34.0 48.0 0.34  97H F 69.0 12.0 38.0 46.0 0.30  02H F 80.0 14.0 32.0 68.0 0.40  06H F 69.0 12.0 31.0 44.9 0.30  72.7 12.7 33.7 53.0 0.33  05H F 65.0 15.0 34.0 43.0 0.29  17H F 64.0 11.0 32.0 46.8 0.31  23H F 85.0 9.0 28.0 85.6 0.31		HEAN		80.0	16.3	35.0		0• 36	60.3	
25H F 75.0 13.0 38.0 49.9 0.40 25H F 100.0 8.0 32.0 49.0 0.31  86.7 12.3 34.0 48.0 0.34  97H F 69.0 12.0 38.0 46.0 0.30  02H F 80.0 12.0 31.0 44.9 0.30  06H F 69.0 12.7 33.7 53.0 0.33  72.7 12.7 33.7 53.0 0.33  17H F 65.0 15.0 34.0 45.8 0.31  23H F 85.0 9.0 28.0 85.6 0.31  71.3 11.7 31.3 58.5 0.30	2 '	H662	щ	85.0	16.0	32.0		0•30	70.0	
25H F 100.0 8.0 32.0 49.0 0.31  86.7 12.3 34.0 48.0 0.34  97H F 69.0 12.0 38.0 46.0 0.30  02H F 80.0 12.0 31.0 44.9 0.30  06H F 69.0 12.7 33.7 53.0 0.33  05H F 65.0 15.0 34.0 43.0 0.29  17H F 64.0 11.0 32.0 46.8 0.31  23H F 85.0 9.0 28.0 85.6 0.31	۷ ۲	913H	4 (	75.0	13.0	38.0		0,40	56.0	
97H F       69.0       12.0       38.0       46.0       0.34         02H F       69.0       12.0       38.0       46.0       0.30         02H F       80.0       14.0       32.0       68.0       0.30         06H F       69.0       12.0       31.0       44.9       0.30         05H F       65.0       15.7       33.7       53.0       0.33         17H F       64.0       11.0       32.0       46.8       0.29         17H F       64.0       11.0       32.0       46.8       0.31         23H F       85.0       9.0       28.0       65.6       0.31         71.3       11.7       31.3       58.5       0.30	7	HC24		100.0	8•0	32.0		0,31	70.0	
97H F 69.0 12.0 38.0 46.0 0.30 02H F 80.0 14.0 32.0 68.0 0.40 06H F 69.0 12.0 31.0 44.9 0.30 72.7 12.7 33.7 53.0 0.33 05H F 65.0 15.0 34.0 43.0 0.29 17H F 64.0 11.0 32.0 46.8 0.31 23H F 85.0 9.0 28.0 85.6 0.31	GROUP M	HEAN		86.7	12.3	34.0		0.34	65.3	
02H F 80.0 14.0 32.0 68.0 0.40 06H F 69.0 12.0 31.0 44.9 0.30  72.7 12.7 33.7 53.0 0.33 05H F 65.0 15.0 34.0 43.0 0.29 17H F 64.0 11.0 32.0 46.8 0.31 23H F 85.0 9.0 28.0 85.6 0.31	'n	<b>197</b> H			12.0	38.0		05-30	61.0	
06H F 69.0 12.0 31.0 44.9 0.36 72.7 12.7 33.7 53.0 0.33 05H F 65.0 15.0 34.0 43.0 0.29 17H F 64.0 11.0 32.0 46.8 0.31 23H F 85.0 9.0 28.0 85.6 0.30	m	802H			14.0	32.0		0,40	62.0	
72.7 12.7 33.7 53.0 0.33 05H F 65.0 15.0 34.0 43.0 0.29 17H F 64.0 11.0 32.0 46.8 0.31 23H F 85.0 9.0 28.0 85.6 0.31 71.3 11.7 31.3 58.5 0.30	m	806H			12.0	31.0		0.30	64.0	
05H F 65.0 15.0 34.0 43.0 0.29 17H F 64.0 11.0 32.0 46.8 0.31 23H F 85.0 9.0 28.0 85.6 0.31 71.3 11.7 31.3 58.5 0.30	GROUP M	EAN			12.7	33.7	53.0	0•33	62.3	
17H F 64.0 11.0 32.0 46.8 0.31 23H F 85.0 9.0 28.0 85.6 0.31 71.3 11.7 31.3 58.5 0.30	4	805H			15.0	34.0	43.0	0.29	82.0	
25H F 85.0 4.0 28.0 85.6 0.31 71.3 11.7 31.3 58.5 0.30	<b>4</b> 4	917H			11.0	32.0	46.8	0,31	76.0	
71.3 11.7 31.3 58.5 0.30	r	4634			9.0	28.0	85.6	0.31	75.0	
	GROUP M	EAN			11.7	31.3	58.5	0° 30	17.11	

TABLE NG. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WFFK 1

SGOT K.UNITS	49.0	45.0	45.0	45.3	55.0	50.0	45.0	50.0	54.0	50.0	44.0	49.3	51.0	55.0	0.64	51.7
BILIRUBIN TOTAL MG\$	0.31	0.25	0.30	0.29	0,30	0.29	0.28	0.29	0• 30	0.30	0.30	0.30	0.30	0.29	0.21	0.27
ALK. PHOS K-A. UNITS	130.4	114.4	103.6	116.1	90.8	153.2	132.0	125.3	101.6	114.4	108.0	108.0	62.0	0 8 9	142.0	1.06
SGPT R-F.	39.0	44.0	45.0	41.7	39.0	41.0	36.0	38.7	41.0	38.0	36.0	38.3	38.0	44.0	35.0	39.0
BUN	15.0	18.0	28.0	20.3	27.0	11.0	11.0	16.3	16.0	18.0	14.0	16.0	19.0	14.0	14.0	15.7
GLUCUSE MG#	94.0	92.0	109.0	98.3	95.0	85.0	135.0	105.0	85.0	115.0	100.0	100.0	0.06	77.0	130.0	0.66
νm×	u i				u.				u.	u_	u_		u	u.	Ľ.	
AN IMAL	787H	804H	930H	MEAN	<b>199H</b>	913H	925н	MEAN	<b>197</b> H	8C2H	806н	MEAN	807H	917H	923H	MEAN
GROUP	٦.	<b>-</b>	-	GROUP	2	7	~	GROUP	m	m	m	GROUP	4	4	4	GROUP MEA
	GLUCUSE BUN SGPT ALK.PHOS TOTAL MG* MG* R-F. K-A.UNITS MG*	S	S HILIRUBIN HAL E GLUCUSE BUN SGPT ALK.PHOS TOTAL HBER X MG% MG% R-F. K-A.UNITS MG% 187H F 94.0 15.0 39.0 130.4 0.31	S	S GLUCUSE BUN SGPT ALK, PHOS TOTAL IBER X MGZ MGZ R-F. K-A.UNITS MGZ MGZ MGZ MGZ MGZ MGZ MGZ MGZ MGZ MGZ	SHLIRUBIN HAL E GLUCUSE BUN SGPT ALK, PHOS TOTAL IBER X MG\$\mathbb{x} MG\$\mathbb{x} MG\$\mathbb{x} R-F_\circ K-A_\circ UNITS MG\$\mathbb{x}  187H F 94.0 15.0 39.0 130.4 0.31 104H F 92.0 18.0 44.0 114.4 0.25 130H F 109.0 28.0 42.0 116.1 0.29	SHLIRUBIN HAL E GLUCUSE BUN SGPT ALK, PHOS TOTAL IBER X MG\$\tilde{x} MG\$\tilde{x} R-F_\circ K-A_\circ UNITS MG\$\tilde{x}  187H F 94.0 15.0 39.0 130.4 0.31 104H F 92.0 18.0 44.0 114.4 0.25 130H F 109.0 28.0 42.0 103.6 0.30  130H F 95.0 27.0 39.0 90.8 0.30 130H F 85.0 11.0 41.0 153.2 0.29	SHLIRUBIN HAL E GLUCUSE BUN SGPT ALK, PHOS TOTAL HBER X MG\$\mathbb{E}\$ MG\$\mathbb{E}\$ R-F. K-A.UNITS MG\$\mathbb{E}\$ HG\$\mathbb{E}\$ HG\$\mathbb	SHLIRUBIN HAL E GLUCUSE BUN SGPT ALK, PHOS TOTAL HBER X MGZ MGZ R-F. K-A.UNITS MGZ HB7H F 92.0 18.0 44.0 114.4 0.25 H30H F 92.0 18.0 42.0 103.6 0.30 H 99H F 95.0 27.0 39.0 90.8 0.30 H3H F 85.0 11.0 41.0 153.2 0.29 H25H F 135.0 11.0 36.0 132.0 0.29	SHLIRUBIN HAL E GLUCUSE BUN SGPT ALK, PHOS TOTAL HBER X MG\$\frac{2}{2} \text{ MG\$\frac{2}{2} \text{ MG\$\frac{2}{2} \text{ R-F}_0 \text{ L130.4} \text{ O.31} \text{ MG\$\frac{2}{2} \text{ MG\$\frac{2}{	SHLIRUBIN SGPT ALK, PHOS TOTAL IBER X MG\$ MG\$ R-F. K-A.UNITS MG\$  187H F 94.0 15.0 39.0 130.4 0.31 104H F 92.0 18.0 44.0 114.4 0.25 130H F 109.0 28.0 42.0 103.6 0.30 13H F 95.0 27.0 39.0 90.8 0.29 13H F 95.0 11.0 41.0 153.2 0.29 13H F 85.0 11.0 41.0 153.2 0.29 15H F 85.0 16.3 38.7 125.3 0.29 62H F 15.0 16.0 41.0 101.6 0.30	SHLIRUBIN HAL E GLUCOSE BUN SGPT ALK, PHOS TOTAL HBER X MG\$\frac{2}{16}\$ R-F. K-A.UNITS MG\$\frac{2}{16}\$  HG\$\frac{2}{18}\$ R-F. K-A.UNITS MG\$\frac{2}{16}\$  HG\$\frac{2}{18}\$ R-F. K-A.UNITS MG\$\frac{2}{16}\$  HG\$\frac{2}{18}\$ R-F. K-A.UNITS MG\$\frac{2}{16}\$  HG\$\frac{2}{18}\$ R-F. K-A.UNITS MG\$\frac{2}{16}\$  HG\$\frac{2}{2}\$ R-F. K-A.UNITS MG\$\frac{2}{2}\$  HG\$\frac{2}{1}}\$  HG\$\frac{2}{1}\$ RG\$\frac{2}{1}\$  HG\$\frac{2}{2}\$  HG\$	SHLIRUBIN SGPT ALK, PHOS TOTAL TOTAL HGE MGE R-F. K-A.UNITS MGE HGE TOTAL HGE MGE R-F. K-A.UNITS MGE HGE TOTAL HGE P4.0 15.0 39.0 130.4 0.35 HGE HGE HGE R-F. K-A.UNITS MGE HGE HGE HGE R-F. K-A.UNITS MGE HGE	SHLIRUBIN SGPT ALK, PHOS TOTAL HGE X MGE R-F, K-A, UNITS MGE 187H F 94.0 15.0 39.0 130.4 0.31 104H F 92.0 18.0 44.0 114.4 0.25 130H F 109.0 28.0 42.0 103.6 0.30 13H F 95.0 27.0 39.0 90.8 0.30 13H F 85.0 11.0 41.0 153.2 0.29 125H F 135.0 11.0 41.0 153.2 0.29 17H F 85.0 16.0 38.0 114.4 0.30 100.0 16.0 38.0 114.4 0.30 100.0 14.0 38.3 108.0 0.30 100.0 16.0 38.3 108.0 0.30	S	SALE ELIGIOSE         GLUCOSE BUN BGPT R-F. R-A.UNITS         ALK.PHOS TOTAL HGS MG\$         ACT LITAL HG\$           18FR X MG\$*         MG\$*         R-F. R-A.UNITS         TOTAL MG\$*           187H F 92.0         18.0         44.0         114.4         0.25           104H F 92.0         18.0         44.0         114.4         0.25           104H F 92.0         18.0         44.0         114.4         0.25           130H F 92.0         18.0         42.0         114.4         0.25           13H F 85.0         11.0         41.0         153.2         0.29           13H F 85.0         16.3         38.7         125.3         0.29           97H F 85.0         16.0         41.0         153.2         0.29           97H F 115.0         16.0         38.0         114.4         0.30           97H F 100.0         16.0         38.0         108.0         0.30           100.0         14.0         36.0         108.0         0.30           17.0         14.0         38.0         0.20         0.30           17.0         14.0         108.0         0.30           11H F 77.0         14.0         0.20         0.30           11H F 77.0 </td

- INDIVIDUAL BLOOD CHEMISTRY VALUES TABLE NO. 3

			RHES	SUS MON	IKEYS R	RHESUS MONKEYS RECEIVING WR WEEK 2	149,024 AD (AX67287)	(AX67287)	FOR TWO		WEEKS
GROUP	AN IMAL NUMBER	SEX	GLUCOSE MG\$	BUN	SGPT R-F.	ALK. PHOS K-A. UNITS	BILIRUBIN TOTAL MG\$	SGOT K. UNITS			
, ha	787H	<b>L</b>	116.0	25.0	31.0	75.2	0,30	56.0			
	804H 930H		96.0 125.0	28.0	27.0	20 CC	0° 30 0° 30	48.0 48.0			
GROUP MEAN	MEAN		112.3	25.3	28.7	73.3	0.28	51.0			
2	799H		109.0	37.0	27.0	49.0	0.25	54.0			
7	913H	u.	100.0	22.0	29.0	66.4	0,33	61.0			
7	925H		125.0	16.	28.0	52.0	0° 30	63.0		-	
GROUP MEAN	MEAN		1111.3	25.0	28.0	55.8	0.29	59.3			
e	<b>197</b> H		86.0	19.0	27.0	47.6	0. 20	65.0			
M	802H	u.	89.0	20.0	24.0	0.09	0.31	63.0			
m	H908		94.0	16.0	25.0	50.4	0.31	58.0			
GROUP MEAN	MEAN		89.7	18•3	25.3	52.7	0.27	62.0			
4	807H		94.0	37.0	28.0	85.6	0.23	58.0			
4	917H	u_	95.0	25.0	35.0	53.2	0.20	67.0			
4	923H		100.0	26.0	25.0	8.06	0. 20	55.0			
GROUP MEAN	MEAN		95.3	29.3	29.3	76.5	0.21	0.09			

WO WEEKS

		S	SERUM	SERUM	SERUM	SERUM	(
GRUUP	NUMBER	π×	SUUTUM MEQ/L	PULASSIUM MEQ/L	CHLUKIUE MEQ/L	CALCIUM	LUZ MEQ/L
-	H006	I	149.0	4.70	108.0	10.8	23.0
-	908H	£	151.0	2.90	113.0	11.2	16.6
-	912H	I	153.0	5.45	117.0	11.3	15.0
GROUP	MEAN		151.0	5,35	112.7	11.1	18.2
7	889H	X	150.0	5.55	117.0	11.4	14.9
7	891H	X	154.0	5.15	114.0	11.4	20.9
7	H606	T	149.0	<b>2</b> * 00	1111.0	11.0	21.0
GROUP	MEAN		151.0	5.23	114.0	11.3	18.9
m	881H	S.	152.0	4.70	115.0	10.3	21.8
ĸ	894H	I	147.0	<b>6.</b> 00	110.0	10.0	17.2
m	897н	I	155.0	4.70	112.0	11.2	22.2
GROUP	MEAN		151.3	4.47	112.3	10.5	20.4
4	892H	I	150.0	4.50	116.0	10.8	18.2
4	895H		156.0	5.10	117.0	12.1	17.5
4	H116	I	151.0	4.80	110.0	10.5	23.0
GROUP	MEAN		152.3	4.80	114.3	11.1	19.6

MEEKS

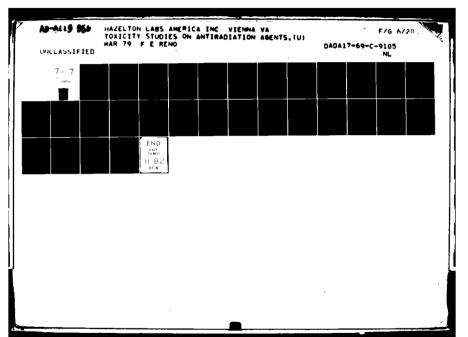
		S	SERUM	SERUM	SERUM	SERUM	,	
GROUP	ANIMAL NUMBER	m ×	SGD I CM	POTASSI UM MEQ/L	CHLORIDE MEQ/L	CALCIUM	CO2 NEQ/L	
-4	H006	T	145.0	4.20	109.5	9.7	21•1	
-	908H	I	148.0	4.20	109.0	9.8	18.8	
	912H	X	150.0	4.90	116.0	10.0	6.6	
GROUP	HEAN		147.7	4.43	111.5	9.8	16.6	
7	889H	I	146.0	4.20	108.0	9.8	21.3	
7	H168	T	147.0	4.40	109.0	6.6	21.9	
7	H606	I	144.0	4.60	112.0	10.2	17.0	
GROUP	MEAN		145.7	4.40	1.09.7	10.0	20.1	
8	881H	I	151.0	4.30	1111.0	10.0	20.9	
~	894H	X	146.0	3.55	110.0	8.8	20.2	
M	897H	Œ	146.0	4.00	107.0	9.8	21.0	
GROUP	MEAN		147.7	3,95	109.3	9.5	20.7	
4	892H	I	149.0	3.80	111.0	10.2	18.0	
4	895H	I	149.0	4.60	114.0	10.0	11.0	
4	911H	E	148.0	4.20	111.5	<b>6.</b>	19.9	
GROUP	MEAN		148.7	4.20	112.2	6*6	16.3	

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS WEEK 2

ANIMAL	νш:	SERUM	SERUM POTASSIUM	SERUM CHLORIDE	SERUM	C 02	
UMBER	×	MEQ/L	MEQ/L	MEQ/L	¥9¥	MEQ/L	
H006	I	152.0	4.50	111.0	10.0	25.1	
908H	I	149.0	3.90	104.0	9.3	22.6	
912H	I	160.0	2.00	116.0	10.4	20.8	
MEAN		153.7	4.47	110.3	6.6	22.8	
889H	I	156.0	4.30	115.0	9.6	14.9	
<b>891H</b>	I	158.0	4.95	112.0	11.2	16.7	
H606	Σ	149.0	3.60	115.0	10.6	21.5	
MEAN		154.3	4.28	114.0	10.4	17.7	
881H	I	150.0	4.10	112.5	9.6	25.1	
894H	I	148.0	3.70	113.0	8.8	24.9	
<b>897</b> H	I	145.0	4.60	112.0	9.6	17.9	
MEAN		147.7	4.13	112.5	9.3	22.6	
	I	147.0	4.00	100.5	11.4	24.0	
895H	E	156.0	4.50	114.5	10.1	21.2	
911H	I	151.0	4.20	109.0	9.5	24.1	
MEAN		151.3	4.23	108.0	10.3	23.1	
	ANIMAL NUMBER 900H 912H 912H 889H 891H 891H 897H 897H 897H	MAAL 10000H 10000H 1000H	MAL E S S E E R X MAL E S O O O O O O O O O O O O O O O O O O	S SERUN BER X MEQ/L 000H M 152.0 08H M 150.0 12H M 156.0 91H M 156.0 97H M 156.0 97H M 149.0 147.7 147.7	S SERUN SERUN BER X MEQ/L NEQ/L  S SERUN SERUN SERUN SERUN CHLORIDE BER X MEG/L M	S SERUN SERUN SERUN SERUN SERUN SERUN CHLORIDE CALCIUM CHORIDE	

O WEEKS

GROUP NUMBER	ANIMAL	αшх	SERUN SODIUM MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG&	C02 MEQ/L
-	787H		149.0	4.60	112.0	10.7	21.0
	804H	щ.	150.0	5.10	113.0		10.
-	930H		148.0	5.05	107.0	11.3	18.0
GROUP	MEAN		149.3	4.92	110.7	10.8	19.0
7	199H		154.0	5.60	114.0	11.6	21.2
7	913H		157.0	5.10	116.0	11.6	2
2	925H	щ	149.0	4.75	109.0	10.9	20.2
GROUP !	MEAN		153.3	5, 15	143.0	11.4	20.8
ю	797H	ц.	154.0	5.20	115.0	11,1	9 10
٣	802H	u.	150.0	4.80	113.0	10.6	20.5
m	806H	u.	150.0	4.70	112.C	10.9	26.1
GROUP P	MEAN		151.3	06*4	113.3	10.9	22.8
4	805H		151.0	5.00	112.0	10.7	74.1
4	917H		151.0	4.40	114.0	900	21.0
4	923Н	ıL.	149.0	5.15	109.0	11.3	19.5
GROUP M	NAM		ני				



EKS

		s	SERUM	SERUM	SERUM	SERUM		
GROUP	ANIMAL	ш	<b>NO 1 00 S</b>	POTASSI UM	CHLORIDE	CALCIUM	C02	
NUMBER	NUMBER	×	MEQ/L	ME Q / L	MEQ/L	₩G%	MEQ/L	
	787H	u_	147.0	4.20	113.0	10.0	16.1	
~	804H	u.	145.0	4.55	111.0	6.6	15.1	
1	930H	ıL.	146.0	4•30	114.0	9.5	13.1	
GROUP	MEAN		146.0	4.35	112.7	8.6	14.8	
~	199H	u,	149.0	4.40	111.0	10.1	22.8	
~	913H	u.	148.0	3.70	113.0	6.6	17.2	
7		u.	147.0	3.90	108.0	8.6	16.5	
GROUP !	MEAN		148.0	4• 00	110.7	6•6	18.8	
ĸ	197H	س	147.0	4.35	107.0	10.5	19.9	
~	802H	u.	146.0	4.10	11110	10.0	18.5	
m	806H	u.	146.0	3.86	109.0	10.0	19.0	
GROUP	MEAN		146.3	4.08	109.0	10.2	19.1	
4		u_	147.0	4.90	111.0	10.3	18.1	
4		u.	147.0	<b>7.</b> 90	112.0	9.8	21.6	
4		u,	149.0	<b>6.</b> 00	111.0	10.0	16.6	
GROUP P	MEAN		147.7	4.60	111.3	10.0	18.8	

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS WEEK 2

ANIMAL NUMBER		SERUN SODIUN MEQ/L	SERUM POTASSIUM MEQ/L	SERUM CHLORIDE MEQ/L	SERUM CALCIUM MG#	C02 MEQ/L
787H 804H	L L	154.0 154.0	<b>4.</b> 20	118.0 113.0	9°6 8°6	17.1 23.0
930H	ı.	158.0	4.60	117.0	10.2	18.2
HEAN		155.3	4.43	116.0	9.8	19.4
199H		151.0	4.35	114.0	10.6	22.8
913H		148.0	4•30	114.0	9.7	15.9
925H	L.	150.0	2.00	110.0	9.8	18.9
MEAN		149.7	4.55	112.7	10.0	19.2
<b>197</b> H		148.0	4.35	110.0	7.6	25.0
802H		147.0	4.20	111.0	7.6	22.9
906	<b>L</b>	145.0	4.80	1111.0	10.9	22.4
MEAN		146.7	4.45	110.7	10.1	23.4
807H	u.	151.0	4.30	112.0	10.2	23.5
917H		153.0	4.15	115.0	10.3	22.0
923H	u.	153.0	4.20	112.0	10.1	21.4
MEAN		152.3	4.22	113.0	10.2	22.3

TABLE NO. 3 - INDIVIDUAL BLOUD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FUR TWO WEEKS
INITIAL

GROUP ANIMAL E NUMBER NUMBER X  1 900H M 1 908H M 1 912H M 2 889H M 2 889H M 2 891H M	PROTE IN						
000H 100H 112H 100H 91H	<b>*</b>	AL BUMIN	ALPHA1	ALPHA2 <b>X</b>	8ETA %	O A M M	AL BUMIN G*
12H 12H 89H 91H	7.11	0.09	5.0	0.6	15.0	11.0	3.30
12H 89H 91H	7.80	53.0	4.0	8.0	20.0	15.0	2.80
89H 91H	7.50	50.0	<b>6.</b> 0	0 • 9	22.0	18.0	2.90
889H 1919 1919	7.47	54.3	4.3	7.7	19.0	14.7	3.00
H168	7.80	53.0	7.0	8.0	19.0	13.0	2.89
1000	7.90	0.09	0.9	8.0	15.0	11.0	2.15
	68 • 9	0.89	4.0	4.0	16.0	0 <b>•</b> 8	3.16
GROUP MEAN	7.53	60.3	5.1	6.7	16.7	10.7	2,91
N HERR	7.39	52.0	3.0	7.5	26.0	11.5	3.11
	8.00	44.0	5.0	0.9	19.0	26.0	2.40
	7.25	58.0	3.0	8.0	20.0	11.0	3.60
GROUP MEAN	7.75	51.3	3.7	7.2	21.7	16.2	3.04
892H M	7.20	55.0	4.0	8.0	19.0	14.0	3.05
	8.69	53.0	7.0	14.0	13.0	13.0	3.51
	7.10	24.0	4.0	0.9	20.0	16.0	2.55
GROUP MEAN	7.66	54.0	5.0	9•3	17.3	14.3	3.04

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 1

1.50				RHES	RHESUS MONKEYS RECEIVING WEEK	S RECEIVIN WEEK	ING MR 1491	WR 149,024 AU (AX67287) 1	X67287) FOR	TWO WEEKS
		v		TOTAL		\$ <b>]</b>	ELECTROPHORESIS-	RESIS	7 - 7 - 7 - 7	TOTAL
	GROUP			PROTEIN	AL BUMIN	ALPHAI	ALPHAZ	BETA	GAMMA	AL BUMIN
· .	NUMBER	NUMBER	J	*	<b>≫</b>	<b>34</b>	34	<b>34</b>	3 <b>4</b>	25
-	~		_	7.00	56.0	3.0	5.0	24.5	11.5	3,12
		₩ H805	_	8.00	45.0	2.0	7.0	38.0	8.0	2.51
	~		_	1.19	47.5	3.5	5.0	28.0	16.0	2.80
	GROUP MEAN	MEAN		7.60	48.5	3.8	5.7	30.2	11.8	2.81
	7		_	7.40	49.0	4.0	0.9	25.0	16.0	2.52
	7	N H168	_	7.41	56.5	3.5	5.0	24.0	11.0	3,31
	~		_	7.11	26.0	3.0	5.0	24.0	12.0	3.19
	GROUP MEAN	MEAN		7.31	53.8	3.5	5.3	24.3	13.0	3.01
- 121	•	881H H	_	7.54	47.0	3.0	0.6	27.0	14.0	2.50
	ĸ	N H768	_	7.79	47.0	3.0	6.5	26.0	17.5	2.30
	M	897H M	_	7.30	0.64	4.0	8.5	22.5	16.0	2.99
	GROUP MEAN	MEAN		7.54	47.7	3.3	8.0	25.2	15.8	2.60
	4	892H H	_	7.00	51.5	4.5	7.0	21.0	16.0	2.90
	4	895H M	_	7.71	55.0	3.0	5.0	25.5	11.5	3.20
	4	911H M	_	16.91	20.0	2.0	0 • 9	28.0	14.0	2.49
	GROUP MEAN	MEAN		7.21	52.2	3.2	0.9	24.8	13.8	2.86

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 2

		U	TOTAL	1	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	-FIECTROPHORESTS-	N FS I S	1	TOTAL
GROUP	AN I MAL NUMBER	n w ×	PROTEIN GX	AL BUMIN	ALPHA!	ALPHA2	BETA	GAMMA	ALBUMIN GX
	900H	I	7.20	51.0	3.0	0.9	27.0	13.0	3.20
-	908H	I	7.35	38.5	3.5	12.0	31.0	15.0	1.85
~	912H	I	8.30	46.0	3.0	0.9	25.0	20.0	3.09
GROUP MEAN	MEAN		7.62	45.2	3.2	8.0	27.7	16.0	2.71
~	889H	X	7.49	48.0	3.5	5.5	26.0	17.0	2.75
~	891H	X	7.83	50.0	2.0	6.5	28.5	13.0	3.72
8	H606	I	7.30	26.0	3.0	 0°0	26.0	10.0	3,35
GROUP MEAN	HEAN		7.54	51.3	2.8	5.7	26.8	13.3	3.27
m	981H	I	7.91	42.0	4.0	0.6	31.0	14.0	2.50
m	894H	I	7.60	43.0	3.0	<b>0°6</b>	23.0	22.0	2,31
m	897H	I	7.19	20.0	3.0	0.9	26.0	15.0	3.15
GROUP MEAN	MEAN		7.57	45.0	3.3	8.0	26.7	17.0	2.65
4	892H	X	7.40	47.0	0.9	10.0	23.0	14.0	2,65
¢,	895H	I	8.11	53.0	3.0	8.0	26.0	10.0	3.21
4	911H	x	7.40	49.5	2.5	5.0	29.0	14.0	2.50
GROUP MEAN	MEAN		7.64	49.8	3°8	7.7	26.0	12.7	2.79

- INDIVIDUAL BLOOD CHEMISTRY VALUES

	ANIMAL	v ш >	TOTAL PROTEIN	AL BUMIN	ALPHA1	ALPHA1 ALPHA2 BET	RESIS BETA	GAMMA	TOTAL ALBUMIN
۰.		t u	74.4	, 64	, r	, ,	9 6	· 0	3.30
•	804H		7.51	20.0	0.7	0 0	24.0		2,71
-	930H	. u	7.01	54.0	4.0	0.6	20.0	13.0	3,15
GROUP	HEAN		7.05	55.8	<b>4.</b> 8	7.3	21.0	11.0	3.05
7	199H	u.	7.61	48.0	4•0	10.0	23.0	15.0	2.80
7	913H	ıL	7.59	58.0	3.5	5.0	19.5	14.0	3.60
7	925H	u.	7.60	47.0	4.0	8.0	25.0	16.0	2,79
GROUP	MEAN		7.60	51.0	3.8	7.7	22.5	15.0	3.06
m	797H		7.90	51.0	3.0	0 8	21.0	17.0	2.89
m	802H		6.80	60.5	0.9	9.5	17.0	12.0	3.01
<b>~</b>	806Н	4	7.00	57.0	5.0	7.0	19.0	12.0	3.10
GROUP	MEAN		7.23	56.2	4.7	8.2	19.0	13.7	3.00
4	HSOR	u.	7.10	51.0	8 0	7.0	18.0	16.0	3.08
*	917H	u.	7.19	55.0	0.9	8.0	20.0	11.0	3.18
4	923H	ш	8.20	43.0	5.0	<b>0•</b> 9	26.0	20.0	2.51
GROUP MEAN	MEAN		7.50	49.7	6.3	7.0	21.3	15.7	2,92

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES
RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS
WEEK 1

	•				-ELECTROPHORES1S	RES18		TOTAL
GROUP	ANIMAL E	PROTEIN	AL BUMIN	ALPHA1 \$	ALPHA2	BETA %	GAMMA *	AL BUM IN G#
-	787H F		56.0	3.0	5.5	26.5	0.6	3.00
-			44.0	4.0	0.9	32.5	13.5	2.50
•		6.91	55.5	4.5	0.4	27.0	0.6	2.90
GROUP MEAN	MEAN	7.14	51.8	3.8	5.2	28.7	10.5	2.80
^	7 HOO7		48.0	5.0	7.0	26.5	13.5	2.81
۰ ۸			52.5	4.5	5.0	23.0	14.0	3,30
٦ د	925H F	8.00	52.0	3.0	0.9	24.0	15.0	2.85
GROUP MEAN	MEAN	7.47	50.8	4.2	0.9	24.5	14.2	2.99
~	7 HTPT		53.0	2.5	0.9	24.5	14.0	2.85
) K			56.0	3.5	5.0	22.5	13.0	3.00
· M	806H F	7.71	52.0	3.0	0.9	26.0	13.0	3.21
GROUP MEAN	MEAN	7.60	53.7	3.0	5.7	24.3	13.3	3.02
4	807H F		51.5	4.0	0.9	28.5	10.0	3,06
•			49.5	4.0	7.5	26.0	13.0	2.90
4	923H F	1.60	47.0	4.5	0*6	27.5	12.0	2.48
GROUP MEAN	HEAN	7,33	49.3	4.2	7.5	27.3	11.7	2.81

TABLE NO. 3 - INDIVIDUAL BLOOD CHEMISTRY VALUES RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWD WEEKS WEEK 2

GROUP NUMBER	ANIMAL E	PROTEIN G\$	AL BUMIN	ALPHA1	ALPHA2 BETA	BETA	GAMA	ALBUMIN 6%
~	787H F	66.9	50.0	2.0	0.6	29.0	10.0	2.91
-		7.80	44.0	3.0	7.0	34.0	12.0	2.70
-	930H F	7.10	51.0	3.0	. 0 • 9	28.0	12.0	3.08
GROUP MEAN	HEAN	7.30	48.3	2.7	7.3	30•3	11.3	2.90
7	799H F	8.09	47.5	2.5	0.9	32.0	12.0	3.01
~	913H F	7.10	57.0	4.0	7.0	20.0	12.0	3.29
8	925H F	8.49	44.5	3.5	7.0	32.0	13.0	2.71
GROUP MEAN	MEAN	7.89	1.67	3.3	1.9	28.0	12.3	3.00
·	797H F	7.50	49.0	3.0	0-9	26.0	16.0	2,80
m	802H F	69.9	58.5	3.0	0.9	22.5	5	3.01
m	806H F	7.80	24.0	2.0	5.0	23.0	16.0	3.30
GROUP MEAN	MEAN	7.33	53.8	2.8	5.1	23.8	13.8	3.04
*	807H F	7.99	46.5	2.5	8.0	30.0	13.0	3.29
•	917H F	7.39	48.0	3.0	0.8	26.0	15.0	3.01
4	923H F	7.90	41.0	3•0	0 • 9	31.0	0.6	2.41
GROUP MEAN	MEAN	7.76	45.2	a c		000		ď

TABLE NO. 4 - URINE ANALYSIS

	SP ERM	FEW			
	BACT SF		***	MANY FEW FEW	333
S	NGS-				Y FEW
WEEKS	INDINGS 4 CRYS	FEN MANY MANY	MANY FEW : FEW	FEUMANY	MANY MANY MANY
R TWO I	HICKOSCOPIC FINDINGSB BC WBC EPITH AMORPH CRYS BACT SPERM		LITTLE	NUCH LITTLE LITTLE	
87) FO	ICKOSCI EPITH	3-4	0-2	4-0	0-2 0-1 0-2
( AX672	#BC	0-1	0~1	0-2 0-1 0-2	0-1
24 AU	RBC	0-2		0-2	
149,0	BILI- Rubin	900	900	000	000
JG WR	PRU- TEIN	000	-00	-0-	0+0
EIVING INITIAL	ACE- TONE	900	000	000	0.0
S RE(	SU- GAR	900	000	000	0 = 0
MONKEYS RECEIVING WK 149,024 AD (AX67287) FOR TWO	SP.GR.	1.032 1.031 1.022	1.031 1.045 1.053	1.035 1.040 1.049	1.030 1.040 1.040
RHESUS	a I	6 - 0	999	<b>0 to 0</b>	81.0
RHE	APPEAR.	YEL	YEL YEL YEL	T YEL YEL YEL	YEL YEL YEL
				>	
	S ANIMAL E NUMBER X	900H H 908H M 912H M	889H M 891H M 909H M	881H M 894H M 897H M	892H M 895H M 911H M
	GROUP		222	<i>ማ</i> ጠ ጠ	444

RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS

	! 5				
	SPER				
	SBACT	FEW FEW MANY		FEW MANY FEW	7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	NDING	FEW	333	MANY FEW FEW	MANY FEW MANY
	PIC FI Amorph	LITTLE MUCH MUCH	LITTLE LITTLE LITTLE	MUCH	MUCH MUCH LITTLE
	HICROSCOPIC FINDINGSBEC WBC EPITH AMORPH CRYS BACT SPERM	0-1			0-2
	EBC E	0-1		1-0	0-1
	RBC	0-1	0-5		
	BILI- RUBIN	000	900	•••	000
~	PRO- TEIN	000	000	000	0 + 0
YEE X	ACE- Tone	000	000	000	040
	SU- GAR	000	000	000	000
	SP.GR.	1.033 1.031 1.031	1.030 1.036 1.032	1.027 1.031 1.030	1.025 1.035 1.040
	a I	သာတတ	<b>\$\$</b> \$\$ \$\$	<b>~</b> ∞ ∞	9 ~ 6
	APPEAR.	T YEL T YEL T YEL	T YEL T YEL T YEL	V T YEL T YEL T YEL	1 YEL 7 YEL 7 YEL
	νшх	III	III	EIE	III
	AN I MAL NUMBER	900H 908H 912H	889H 891H 909H	881H 894H 897H	892H 895H 911H
	GROUP NUMBER		000	m m m	444

TABLE NO. 4 - URINE ANALYSIS RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWG WEEKS WEEK 2

BACT SPERM				
SBACT	FEE		FEX	MANY
NDING	FEW FEW MANY	FEW		FEW MANY MANY
BC WBC EPITH ANDRPH CRYS BACT SPERM	MUCH FEW LITTLE	LITTLE Much Much	MUCH LITTLE MUCH	LITTLE MUCH
II CROS C EP ITH		0-5	5-10 0-4 0-2	0-1 0-1 5-6
WBC			0-1	0-1 0-3
RBC			. 1-0	
BILI- Rubin	000	000	000	000
PRO- Te i n	0-0	000	000	000
ACE- TONE	00-	000	000	000
SU- GAR	000	000	000	000
SP.GR.	1.041 1.027 1.032	1.035 1.043 1.040	1.035 1.041 1.032	1.010 1.028 1.043
ø I	Q. 40 80	8 7 8	<b>∞</b> ∞ ∞	<b>~</b> 66
APPEAR.	T YEL T YEL T YEL	T YEL V T YEL T YEL	V T YEL T YEL V T YEL	T L YEL T YEL V T YEL
νшх	III	TTT	III	III
AN I MAL NUMBER	900H 908H 912H	889H 891H 909H	881H 894H 897H	892H 895H 911H
GROUP NUMBER		000	ммм	444

TABLE NO. 4 - URINE ANALYSIS RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FUR TWO WEEKS INITIAL

	SPERM				
	BACT	7 7 7 7 7 7 7 7 7	# # 3 3	F WANY WANY	333
	DINGS	MANY FEW MANY	3	MANY MANY FEW	
	MICROSCOPIC FINDINGSBERM	MUCH LITTLE	MUCH MUCH LITTLE	LITTLE	LITTLE MUCH MUCH
	CROSC( EPITH	5-10	3-7	0-2 7-10 8-10	0-4 0-2 0-2
	WBC	1-3 6-12 1-3	4-8	6-12 2-3	3-5
	RBC	0-2			15-20
	BILI- RUBIN	000	000	000	000
1	PRO- TEIN	000	40+	00-	000
	ACE- TUNE	000	007	000	000
	SU- GAR	000	000	000	000
	SP.GK.	1.030 1.045 1.046	1.030 1.031 1.029	1.039 1.040 1.035	1.036 1.040 1.031
	a I	9 ~ ~	, 0~5	L 8 L	7 9 7
	APPEAR.	T YEL V T YEL T YEL	T YEL VT L YEL T YEL	T YEL T YEL T YEL	T YEL T YEL T YEL
	νшх	<b></b>	u u u	<b></b>	TT TT
	AN I MAL NUMBER	787H 804H 930H	799H 913H 925H	797H 802H 806H	807H 917H 923H
	GRUUP NUMBER		8 8 8	ммм	444

	SPERM				
		HANY MANY FEW	MANY FEN FEN	MANY FEE FEE	FEX FANY
WEEKS	NDINGS CRYS	FEE	FE	33	FEW MANY FEW
FOR TWO W	MICROSCOPIC FINDINGS BC WBC EPITH AMORPH CRYS BACT	LITTLE MUCH MUCH	NUCH NUCH NUCH	HUCH HUCH HUCH	
	I CROS CC EP I TH	0-3	2 0 1 1 4 1 6	3-5	0-5
YS I S ( A X 6 7 2 )	MBC	9-4	0-2	2-3	0-2
ANAL 4 AU	RBC	0-5		4-6	
- URINE ANALYSIS 149,024 AD (AX67287)	BILI- RUBIN	000	000	000	000
ุั≆⊶	PRO- TE IN	000	000	0 <b>0 -</b>	000
E NO.	ACE- TONE	000	000	000	000
TABI S REC	SU- GAR	000	000	000	000
TABLE NO. 4 MONKEYS RECEIVING WEEK	SP.GR.	1.022 1.035 1.048	1.050 1.022 1.030	1.023 1.030 1.050	1.020 1.024 1.028
	o I	` co o- co	ထထင္	800	8 - 1
RHESUS	APPEAR.	YEL YEL T YEL	D YEL L YEL YEL	YEL Yel O Yel	YEL YEL YEL
	₹	<b>⊢⊢&gt;</b>			
	ж К П	TIT	ш ш ш т т т	<u> </u>	<b></b>
	AN I MAL NUM BER	787H 804H 930H	799H 913H 925H	797H 802H 806H	807H 917H 923H
	GROUP NUMBER	, and , and	~ ~ ~	M M M	444

TABLE NO. 4 - URINE ANALYSIS RHESUS MONKEYS RECEIVING WR 149,024 AD (AX67287) FOR TWO WEEKS WEEK 2

SPERM				
BACT	333		33	
UDING: CRYS			FEW FEW MANY	FEW
MICROSCOPIC FINDINGSBEC WBC EPITH AMORPH CRYS BACT SPERM	NUCH NUCH LITTLE	MUCH	MUCH	LITTLE
ICROSC EPITH	2-3	3-5	0-2 5-10 4-5	0-1 0-5
WBC	0-1 3-5 0-3	2-4	5-10 0-2 8-12	4-7 2-3 5-10
RBC		10-12		
BIL I- Rubin	000	000	000	000
PRO- TEIN	000	000	000	000
ACE- TONE	000	000	000	000
SU- GAR	000	000	000	000
SP.GR.	1.033 1.043 1.038	1.030 1.030 1.030	1.032 1.035 1.033	1.025 1.030 1.037
Q I	∞ ~ ∞	8	<b>~</b> ~ ~ ~	<b>\$</b>
APPEAR.	V T YEL T YEL T YEL ·	T YEL T YEL T YEL	T YEL V T YEL V T YEL	T YEL F YEL V T YEL
SEX	444	<b></b>	11. 12. 12.	**
AN IMAL NUMBER	787H 804H 930H	799H 913H 925H	797H 802H 806H	807H 917H 923H
GROUP	ल <b>ल</b> ल ं	~ ~ ~	m m m	444

TABLE NO. 5 - TERMINAL BODY WEIGHTS, ORGAN WEIGHTS, AND ORGAN/BODY WEIGHT RATIOS

SPECIES AND STRAIN - RHESUS MONKEYS INTERVAL - TWO WEEKS MATERIAL - WR 149,024 AD ROUTE OF ADMINISTRATION - INTRAVENOUS

	EEN PATTO	PCT 0-1181	0.1314		· · · · · · · ·	588
	SPLEEN WEIGHT	3.070 5.450	3,857			
	LIVER RATIO	PCT 2.9938 3.3172	2.0246	ES RATIO PCT	0.0346 0.0706 0.2835	0.1296
	SHT	77.840 89.565	83,472	TESTES WEIGHT RA	0.900 1.905 11.625	4.810
TROL	HEART RATIO PCT	0.4725 0.5291	0.4828	ALS RATIO PCT	0.0212 0.0261 0.0129	0.0201
MALES - CONTROL	HE, WE 1GHT	12.285 14.285 18.325	14.965	ADRENALS Weight R.	0.550 0.705 0.530	0.595
•	ROID RATIO PCT	0.0146 0.0226 0.0148	0.0173	EYS RATIO PCT	0.3760 0.6639 0.3572	0.4657
	THYRO] WEIGHT G	0.380 0.610 0.605	0.532	KIDNEYS Weight Rai G PC	9.775 17.925 14.645	14.115
	TERM. BODY Weight Kg	2.60.2.70	3.13	TERM. BODY Weight Kg	2.60 2.70 4.10	3•13
	ANIMAL ND.	900H 908H 912H	MEAN	ANIMAL No.	900H 908H 912H	

Table No. 5 - Continued

MALES - 5.0 MG/KG/DAY

Z	RATIO PCT	0.1303	1100	0.2035	0.1510					58	79
SPI FEN	WE IGHT G	4-170	300.4	4.885	4.050						
LIVER	RAT10 PCT	2.6653	2,2552	2,3527	2.4244	ES RATIO PCT	0.0469		0.0425	0.0447	<b>D</b> •
7	WE IGHT 6	85.290	58,635	56.465	161.99	TESTES WEIGHT I	1.500	0.0	1.020	1.260	NOT RECORDE
HEART	RATIO PCT	0,3905	0.5000	0.5010	0.4638	JALS RATIO PCT	0.0205	0.0229	0.0273	0.0235	AN WEIGHT
HE.	WE IGHT G	12,495	13.000	12.025	12,507	ADRENALS WEIGHT R.	0.655	0.595	0.655	0.635	RATIO INDICATE ORGAN WEIGHT NOT RECORDED.
ROID	RATIO PCT	0.0144	0.0206	0.0185	0.0178	NEYS RATIO PCT	0.3544	0.4590	0.4717	0.4284	
THYRO	WE I GHT G	0.460	0.535	0.445	0.480	KIDNEY Weight G	11.340	11.935	11.320	11.532	AN WEIGHT /
TERM. BODY	WEIGHT KG	3.20	2.60	2.40	2.73	TERM. BODY Weight Kg	3.20	2.60	2.40	2.73	NOTE - ZEROS FOR ORGAN WEIGHT AND
ANIMAL	<b>.</b>	<b>889H</b>	89 1H	H606	MEAN	ANIMAL NO.	H688	891H	H606	MEAN	NOTE - 2

Table No. 5 ~ Continued

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ANIMAL	TERM. BODY	THY	THYROID	HE	HE AR T	•	į		
Ē	WEIGHT KG	WEIGHT G	RATIO PCT	WE IGHT G	RATIO PCT	LIVER WEIGHT G	VER RATIO PCT	SPLEEN	~
881H 894H 897H	2.80 3.10 3.30	0.730 0.495 0.480	0.0261 0.0160 0.0145	13.790	0.4925 0.3865 0.4341	75.295	2.6891	3.105 3.245	0.1109 0.1047
HEAN	3.07	0.568	0.0189	13,365	0.4377	71.692	2.3550	4.190 3.513	0.1270
ANIHAL NO.	TERM. BODY Weight Kg	KIDNEYS Weight R.	LEVS RATIO PCT	ADRENALS WEIGHT RAT	ALS RATIO PCT	TESTES WEIGHT RA	ES RATIO		
881H 894H 897H	2.80 3.10 3.30	10.755 12.240 10.895	0.3841 0.3948 0.3302	0.615 0.665 0.685	0.0220 0.0215 0.0208	1.195 1.185 1.520	PCT 0.0427 0.0382		_
MEAN	3.07	11.297	0.3697	0.655	0.0214	020-1	0.0461		5

Table No. 5 - Continued

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ANIMAL	TERM. BODY	THYRO		HEART	IRT	17	LIVER	Nam ION	2	
	K G	9 9	PCT	WEIGHT G	RATIO PCT	WE IGHT G	RAT10 PCT	WEIGHT 6	RATIO	•
892H	2.20	0.345	0.0157	12,360	0.5618	62+005	2,8184			-
911H	3.30	0.705	0.0252 0.0115	15,185	0.5423	57.250	2.0446	5.985	0.1364 0.2138	
MEAN	ŗ					001.61	791757	4.855	0.1471	-
	77.7	0.477	0.0175	13,865	0.5100	64.118	2.3594	4.613	0.1657	· • <b>-</b> ·
ANIMAL NO.	TERM. BODY Weight	KIDNEYS WEIGHT R	AT10	ADRENALS WEIGHT RAT	ALS	TESTES	ËS			
	y V	<b>9</b>		9	PCT	6 6	PCT			
892H 895H	2.20	11.190	0.5086	0.465	0.0211	1.240	0.0564			
911H	3,30	11.775	0.3568	0.445 0.455	0.0159	1.235 2.005	0.0441		- Veen	
HEAN	2.17	11.542	0.4273	0.455	0.0169	1.493	0.0537		59	

Table No. 5 - Continued

FEMALES - CONTROL

KG G PCT G P	ANIMAL NO.	TERM. BODY	THYROID R.	OID	HEART	IRT PATTO	LIVER	ER	SPL EEN	EN	
3-20 2-90 2-60 2-60 0-625 0-6216 0-625 0-6216 0-625 0-6216 0-625 0-6216 0-6273 0-627		KG	G	PCT	9	PCT	5	PCT	4 E 16 H 1	PCT	
TERM. BODY KIDNEYS ADRENALS C.5767 6.205 2.7657 4.610  TERM. BODY KIDNEYS ADRENALS C.4944 72.782 2.5080 3.858  WEIGHT WEIGHT RATIO WEIGHT RATIO C. 2.90 0.0067  3.20 11.565 0.3614 0.485 0.0174 0.195 0.0067  2.90 12.565 0.4333 0.545 0.0210 0.225 0.0087  2.90 11.672 0.4044 0.512 0.0178 0.610 0.0198	787H	3.20	0.305	0.0095	14.300	6944.0	76.940	2.4044	4-395	0.1373	
TERM. BODY KIDNEYS ADRENALS 0.4944 72.782 2.5080 3.858  WEIGHT WEIGHT RATIO WEIGHT RATIO G PCT G PCT G PCT G PCT C.195 0.0067  3.20 11.565 0.3614 0.485 0.0152 1.410 0.0441 C.290 12.565 0.4187 0.545 0.0210 0.225 0.0067  2.90 11.672 0.4044 0.512 0.0178 0.610 0.0198	804H	2.90	0.625	0.0216	16,635	0.5736	80.205	2, 7657	4-610	0.1590	
TERM. BODY KIDNEYS ADRENALS Ov4944 72.782 2.5080 3.858  TERM. BODY KIDNEYS ADRENALS OVARIES WEIGHT RATIO WEIGHT RATIO G PCT  3.20 11.565 0.3614 0.485 0.0152 1.410 0.0441 2.90 12.565 0.4333 0.505 0.0174 0.195 0.0067 2.60 10.885 0.4187 0.545 0.0210 0.0198	930H	2.60	0.380	0.0146	12.030	0.4627	61.200	2,3538	2.570	0.0988	
TERM. BODY KIDNEYS ADRENALS OVARIES WEIGHT WEIGHT RATIO WEIGHT RATIO  WEIGHT RATIO WEIGHT RATIO  WEIGHT RATIO  WEIGHT RATIO  WEIGHT RATIO  WEIGHT RATIO  O.485 O.0152 I.410 O.0441  2.90 I2.565 O.4333 O.505 O.0174 O.195 O.0067  2.60 I0.885 O.4187 O.545 O.0210 O.225 O.0087  2.90 I1.672 O.4044 O.512 O.0178 O.610 O.0198	MEAN	2.90	0.437	0.0152	14.322	0.4944	72.782	2.5080	3.858	0.1317	
MEIGHI NEIGHI RATIO MEIGHT RATIO  KG G PCT G PCT  H 3.20 11.565 0.3614 0.485 0.0152 1.410 0.0441  H 2.90 12.565 0.4333 0.505 0.0174 0.195 0.0067  H 2.60 10.885 0.4187 0.545 0.0210 0.225 0.0087  Z.90 11.672 0.4044 0.512 0.0178 0.610 0.0198	ANIHAL	TERM. BODY	NO I X	EYS	ADREN	IALS	OVAR	IES			
H 3.20 11.565 0.3614 0.485 0.0152 1.410 0.0441 2.90 12.565 0.4333 0.505 0.0174 0.195 0.0067 H 2.60 10.885 0.4187 0.545 0.0210 0.225 0.0087 2.90 11.672 0.4044 0.512 0.0178 0.610 0.0198		WEIGHI KG	WE I GHI G	RATIO	WE I GHT G	RATIO PCT	WE IGHT G	RATIO PCT			
H 2.90 12.565 0.4333 0.505 0.0174 0.195 0.0067 H 2.60 10.885 0.4187 0.545 0.0210 0.225 0.0087 2.90 11.672 0.4044 0.512 0.0178 0.610 0.0198	<b>787</b> H	3.20	11.565	0.3614	0.485	0.0152	1.410	0.0441	_	•	
H 2.60 10.885 0.4187 0.545 0.0210 0.225 0.0087 2.90 11.672 0.4044 0.512 0.0178 0.610 0.0198	804H	2.90	12,565	0.4333	0.505	0.0174	0.195	0.0067			
2.90 11.672 0.4044 0.512 0.0178 0.610 0.0198	930H	2.60	10.885	0.4187	0.545	0.0210	0.225	0.0087		5	
	MEAN	2.90	11.672	0.4044	0.512	0.0178	0.610	0.0198		92	

Table No. 5 - Continued

FEMALES - 5.0 MG/KG/DAY

TER:	TERM. BODY	THYROID	010	HEART	RT	LIVER	/ER	SPLEEN	EN
# # # # # # #	Ē.,	## 1 GH 1	PCT	We IGH I G	RATIO PC1	WE IGHT G	RATIO PCT	WEIGHT G	RATIO PCT
m	3.10	0.465	0.0150	15.700	0.5065	79.855	2.5760	4.185	0.1350
~	09•	0°360	0.0138	12.840	0.4938	62.205	2,3925	2.810	0.1081
101	3.00	0.715	0.0238	15.775	0.5258	73.140	2.4380	5.215	0.1738
•	2.90	0.513	0.0176	14.772	0.5087	71.733	2.4688	4.070	0.1390
TERM	TERM. BODY	KIDNEYS	EYS	ADRENALS	ALS	OVARIES	IES		
7	WE I GHT K G	WEIGHT G	RATIO PCT	WE IGHT G	RATIO PCT	WEIGHT G	RAT 10 PCT		
	3.10	12.550	0.4048	0.645	0.0208	0.160	0.0052		
•	2.60	10.780	0.4146	0.685	0.0263	0.105	0.0040		
•••	3.00	12.380	0.4127	0.800	0.0267	0.290	1600.0		
	2.90	11.903	0.4107	0.710	0.0246	0.185	0.0063		54

Table No. 5 - Continued

FEMALES - 10.0 MG/KG/DAY

ANIMAL	TERM. BODY	THY	THYROID	HE/	HEART	LIVER	/ER	NA ION	2
*0*	WEIGHT KG	WEIGHT G	RATIO PCT	WE IGHT G	RATIO PCT	WE IGHT G	RATIO PCT	WE IGHT G	RATIO
H197	2.60	00400	0.0154	15.045	0.5787	74.020	2.8469	2,925	0.1126
802H	3.50	0.685	0.0196	15.895	0.4541	78.100	2,2314	4.195	0.1199
E 000	3•30	0.445	0.0135	17.920	0.5430	71.580	2.1691	2.495	0.0756
MEAN	3.13	0.510	0.0161	16.287	0.5253	74.567	2.4158	3,205	0.1027
ANI MAL ND•	TERM. BODY WEIGHT KG	KIDNEYS WEIGHT R	IEVS RATIO PCT	ADRENALS WEIGHT	HALS RATIO	OVARIES WEIGHT R	RATIO		
	?	•	5	٥	ב ב	פי	PCT		
H161	2.60	11.765	0.4525	0.800	0.0308	0.160	0.0062		
H708	3.50	13.900	0.3971	009.0	0.0171	0.320	0.0091		
H908	3•30	16.120	0.4885	0.705	0.0214	0.250	0.0076		
MEAN	3.13	13.928	0.4460	0.702	0.0231	0.243	0.0076		1

Table No. 5 - Continued

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FEMALES
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	RAT 10 PCT	0.114C 0.0935 0.1581	0.1219			595
7	RA! PC	000	0.1			. •
ADA 100	WEIGHT G	3.535 2.805 5.060	3.800	•		
LIVER	RATIO PCT	2.5990 2.4707 2.3669	2.4789	NES RATIO PCT	0.0076 0.0060 0.0045	0•0000
	WE IGHT G	80.570 74.120 75.740	76.810	OVARIES WEIGHT RAT G PC	0.235 0.180 0.145	0.187
ART	RATIO PCT	0.5177 0.4457 0.4811	0.4815	WALS RATIO PCT	0.0189 0.0175 0.0228	0.0197
HEART	WE IGHT G	16.050 13.370 15.395	14.938	ADRENALS WEIGHT RA	0.585 0.525 0.730	0.613
THYROID	RATIO PCT	0.0166 0.0165 0.0272	0.0201	MIDNEYS IT RATIO PCT	0.3765 0.3925 0.4228	0,3973
THY	WEIGHT G	0.515 0.495 0.870	0.627	M I DI W E I GHT G	11.670 11.775 13.530	12.325
TERM. BODY	WEIGHT KG	3.10 3.00 3.20	3.10	TERM. BODY Weight Kg	3.10 3.20 3.20	3.10
ANIMAL		807H 917H 923H	MEAN	ANTHAL NO.	807H 917H 923H	NEAN

## KEY FOR INCIDENCE TABLE

- P = Present
- N = No Section
- A = Autolysis
- X = Not Remarkable
- 1 = Minimal
- 2 = Slight
- 3 = Moderate
- 4 = Moderately Severe/High
- 5 = Severe/High

## DETAILED HISTOPATHOLOGY INCIDENCE TABLE

	<u>§</u>	Groups	<del></del>
Males	Animal 900H 908H 912H	881H 881H 881H 897H	892H
THYROID Level of activity	3 2 2		3 2 2
ADRENAL Mineralization	1 X X		x x 1
MESENTERIC LYMPH NODE Periadenitis Pigmentation Parasites Increase in neutrophils Adenitis	x x		X 4 2 P
HEART Focal endocarditis Focal myocarditis	x x x		ххх
SPLEEN Pigmentation Extramedullary hematopoiesis Congestion Lymphoid hyperplasia	1 2 1 2 2	1	x x 1

	NO	Groups	
	1 +	2 3	4
Females	Animal 804H 930H 787H	799H 913H 925H 797H 802H	807H 917H 923H
THYROID Level of activity	3 2 2		2 3 2
ADRENAL Mineralization	x 1 3		X 4 2
MESENTERIC LYMPH NODE Periadenitis Pigmentation Parasites Increase in neutrophils Adenitis	x x 3		X 4
HEART Focal endocarditis Focal myocarditis	х 1 3		ххх
SPLEEN Pigmentation Extramedullary hematopoiesis Congestion Lymphoid hyperplasia	x x 2		x x 2

Well-r	Animal No. 900H   H 912H   H	Groups  2 3  H H H H H H H H H H H H H H H H H H	892H   1   1   1   1   1   1   1   1   1
Males	<u> </u>		
GALL BLADDER	ххх		ххх
LIVER Hepatocyte vacuolation Pericholangitis Focal lymphoid infiltration	1-2 1 1 2	1 2 X	x 1 1
KIDNEY Chronic interstitial nephritis	x x	x x x x x x	1 1 X
STOMACH Papillary mucosal hyperplasia Gastritis Parasite	x x 3		ххх
SMALL INTESTINE Enteritis Parasite	ххх		1 P
LARGE INTESTINE Colitis Serositis	x x		2 X X

	ON	Groups	
	1 -	2 3	4
Females	Animal 804H 930H 787H	799H 913H 925H 797H 802H 806H	807H 917H 923H
GALL BLADDER	ххх		ххх
LIVER  Hepatocyte vacuolation Pericholangitis Focal lymphoid infiltration	x 1	X 2 2 1 1 1 2 1 1 1	1 1 1 1 1
KIDNEY Chronic interstitial nephritis	x x	x x x - x x x	x x
STOMACH Papillary mucosal hyperplasia Gastritis Parasite	x x 2	5 P	x x x
SMALL INTESTINE Enteritis Parasite	ххх		x x x
LARGE INTESTINE Colitis Serositis	ххх		X 4 4

	Groups 3	4_
Males	9008H 908H 912H 909H 889H 881H 894H	892H 895H 911H
PANCREAS Focal lymphoid hyperplasi Pancreatitis	x x x	ххх
URINARY BLADDER Cystitis	x x 3	x x 2
TESTIS Prepubital	P P P	P P P
OVARY Cysts		
BONE MARROW Increase cellularity Decrease cellularity	х х	х N 3

LUNG
Lungmite
Pleural thickening

BRAIN Focal fibrosis

	No.					Groups								
		I				_2			3			4		
Females	Animal	804H	930H	18711	1991	91311	92511	197н	802н	80611	807н	91711	92311	
PANCREAS Focal lymphoid hyperplasi Pancreatitis	.a	х	x	2							х	3	x	
URINARY BLADDER Cystitis		x	x	х							x	x	2	
TESTIS Prepubital														
OVARY Cysts		N	x	P							x	x	x	
BONE MARROW Increase cellularity Decrease cellularity		x	x	x							2	x	2	
LUNG Lungmite Pleural thickening					3								P	
BRAIN Focal fibrosis						P								

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